Articles

Daphniphyllum Alkaloids. 10. Classical Total Synthesis of Methyl Homodaphniphyllate[1]

Clayton H. Heathcock,* Steven K. Davidsen,[2a] Sander G. Mills,[2b] and Mark A. Sanner[2c]

Department of Chemistry, University of California, Berkeley, California 94720

Received August 6, 1991

Details for the first total synthesis of a *Daphniphyllum* alkaloid are presented. The synthesis required a total of 15 steps from the known keto acid **4** and followed the course **4** → **10** → **11** → **16** → **20** → **24** → **25** → **27** → **29** → **36** → **46** → **47** → **48** → **49** → (±)-**2**; the overall yield was about 1.1%. The first three rings were assembled from keto acid **4** and ketal amine **8**, which were coupled to form amide **10**. This material was isomerized under acidic conditions to the tricyclic ketal lactam **11**. The masked propionic acid side chain was introduced by alkylation of the lithium enolate of **11** to give **16**. Although the remaining skeletal carbons could be added to **16** in a Michael addition of its lithium enolate to enone **13**, keto amide **17** could not be cyclized to the desired tetracyclic system. However, the related keto thioamide **24**, lacking the isopropyl group, was smoothly cyclized to the tetracyclic, vinylogous amide **25**. Enone **25** was transformed into its isomer, **29**, by a four-step sequence of steps. Treatment of **29** with aqueous acid caused hydrolysis of the ketal and aldolization to give **30**, which was isomerized to **31** under basic conditions. Compound **31** was the first synthetic material having the characteristic pentacyclic skeleton of daphniphylline. For introduction of the remaining carbons, the lithium enolate **29** was treated with acetaldehyde, and the resulting aldol subjected to strongly acidic conditions to obtain the desired pentacycle **36**, accompanied by a small amount of the hexacyclic byproduct **37**. The final carbon could be installed by addition of lithium dimethylcopper to **36**, but the product was a mixture of the diastereomeric diketones **43** and **44**. These two isomers were found to be in facile equilibrium, even under chromatographic conditions. Furthermore, we were unable to remove the carbonyl groups, apparently because one of the carbonyl groups is exceedingly hindered. Therefore, the final carbon was added and the carbonyl groups removed by an indirect method. The enolate ion resulting from the cuprate reaction on **36** was trapped with diethyl phosphorochloridate to obtain enol phosphate **46**. After converting the other carbonyl group into an enol phosphate, compound **47** was subjected to lithium in ethylamine to cleave the two vinyl phosphate groups and the benzyl group. In addition, one of the two double bonds was reduced; compound **48** was obtained in 64% yield. The remaining double bond proved to be very resistant to catalytic hydrogenation conditions; reduction occurred only at high pressure (1800 psi), high temperature (120 °C), and long reaction time (20 h). With Rh on Al_2O_3, amino ester **50** gave completely the undesired stereochemistry, affording **51**. However, Pearlman's catalyst, $Pd(OH)_2$ on carbon, gave a 1:1 mixture of the two isomers when these conditions were applied to amino acid **49** in methanolic solution; **51** and racemic methyl homodaphniphyllate ((±)-**2**) were formed in a ratio of 1:1. The two isomers are readily separated by silica gel chromatography.

The deciduous tree Yuzuriha (*Daphniphyllum macropodum* Miquel) derives its name from an unusual growth habit; the old leaves do not wither and fall away until the year's new leaves are fully developed and functioning.[3] Although alkaloidal material was first isolated from *D. macropodum* in 1909,[4] it was not until 1966 that the structure of a pure substance, daphniphylline, was elucidated by X-ray crystallographic analysis.[5] Since that time, more than three dozen squalene-derived alkaloids, obviously related in a biogenetic sense, have been isolated from *D. macropodum*, *D. teijsmanni* Zollinger ("Hime-Yuzuriha"), *D. humile* Maxim ("Ezo-Yuzuriha"), *D. gracile* Gage, and *D. glaucescens* Bl.[6] *D. macropodum* has traditionally been included in Euphorbiaceae, although some botanists place it in a separate family, Daphniphyllaceae.[7] There was a recent report of isolation of a closely related alkaloid, bukittinggine, from the leaves of *Sapium baccatum* (Roxb.) Ridley (Euphorbiaceae).[8]

Daphniphylline (**1**) is, in many ways, the archetypal *Daphniphyllum* alkaloid. It is the most wide-spread and most abundant and was the first to have its structure determined. Its triterpenoid skeleton embodies two domains, a nitrogen-containing pentacycle and a 2,8-dioxabicyclo[3.2.1]octane unit. It is accompanied in *D. macropodum* by a minor alkaloid, methyl homodaphniphyllate (**2**). We selected alkaloid **2** as our initial synthetic target. In this paper, we report the details of a synthesis of **2**, designed and executed along classical lines.[9] Sub-

(1) (a) For part 9, see: Heathcock, C. H.; Piettre, S.; Kath, *J. Pure Appl. Chem.* **1990**, *62*, 1911. (b) For part 8, see: Stafford, J. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 5433.

(2) Present address: (a) Dept. 47J, AP10, Abbott Laboratories, Abbott Park, IL 60064; (b) P.O. Box 2000, R121-255, Merck Sharp & Dohme Research Laboratories, Rahway, NJ 07065; (c) Sterling Winthrop, Inc., 81 Columbia Turnpike, Rensselaer, NY 12144.

(3) *Yuzuru* means (approximately) "to transfer from hand to hand" and *Ha* means "leaves". The supplementary material to this paper contains a Japanese poem entitled *Yuzuri-ha* by the poet Suimei Kawai, both in the original Japanese and an English translation prepared by Dr. Yasuhiko Inoue of the Sumitomo Chemical Company.

(4) Yagi, S. *Kyoto Igaku Zasshi* **1909**, *6*, 208.

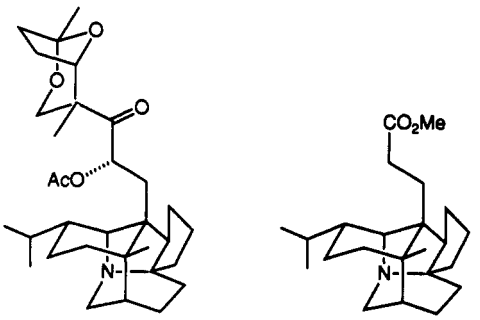
(5) Sakabe, N.; Hirata, Y. *Tetrahedron Lett.* **1965**, 965.

(6) For reviews on *Daphniphyllum* alkaloids, see: (a) Yamamura, S.; Hirata, Y.; In *The Alkaloids*, Vol. 15; Manske, R. H. F., Ed.; Academic Press: New York, 1975; p 41. (b) Yamamura, S.; Hirata, Y. *Int. Rev. Sci.: Org. Chem., Ser. Two* **1976**, *9*, 161. (c) Yamamura, S. In *The Alkaloids*, Vol. 29, Brossi, A., Ed.; Academic Press: New York, 1986; p 265.

(7) (a) Hutchinson, J. *Evolution and Phylogeny of Flowering Plants*; Academic Press: New York, 1969; p 141. (b) Hegnauer, R. *Chemotaxonomie der Pflanzen*, Vol. 4; Birkhaeuser: Basel, 1966; pp 9-11. See also: (c) Gibbs, R. D. *Chemotaxonomy of Flowering Plants*, Vol. III; McGill-Queen's University Press: Montreal, 1974; pp 946, 1347-48.

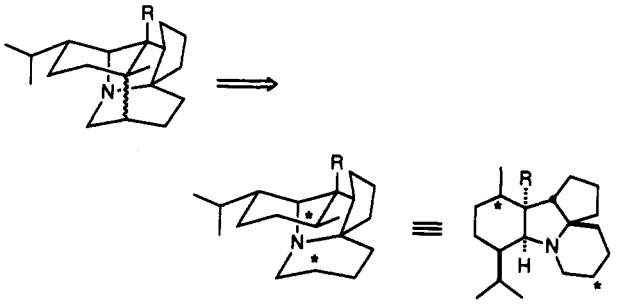
(8) Arbain, D.; Byrne, L. T.; Cannon, J. R.; Patrick, V. A.; White, A. H. *Aust. J. Chem.* **1990**, *43*, 185.

0022-3263/92/1957-2531$03.00/0

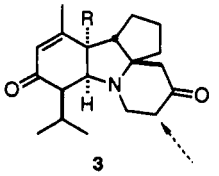


sequent to this work, we discovered a highly efficient, biomimetic route to the basic *Daphniphyllum* alkaloid skeleton and have employed this route in the synthesis of several members of the family, including **2**. This work is detailed in succeeding papers in this series.

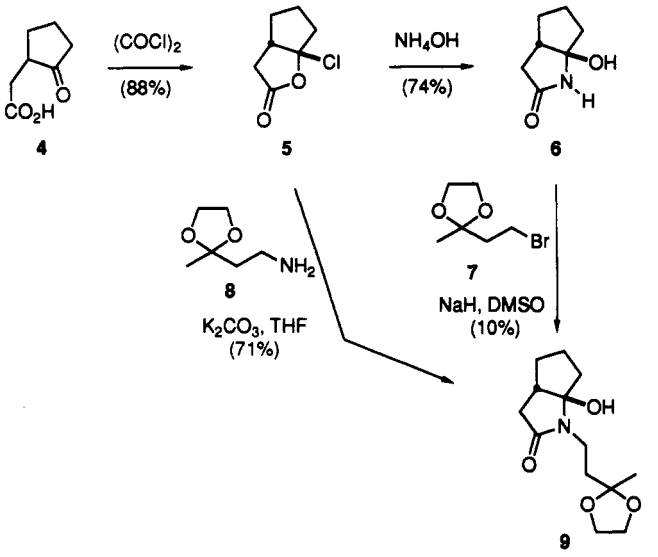
In our initial analysis of the pentacyclic skeleton of **2** we employed "network analysis", more or less as outlined by Corey,[10] and identified the strategic bond disconnection shown[11]



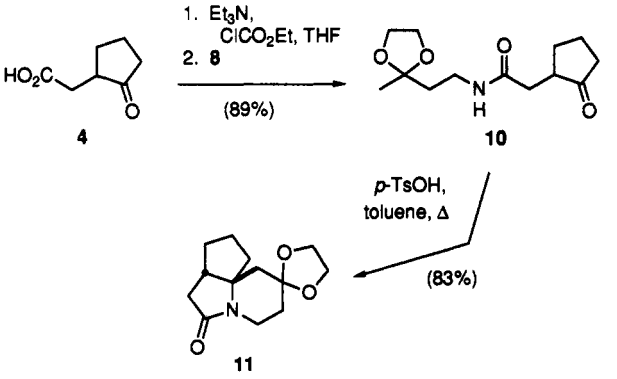
Network analysis only provides guidance with regard to general strategies for construction of the target skeleton. When an attractive skeletal intermediate has been found by this method, it is necessary to equip it with functional groups so that the strategic bond can be formed by some reliable reaction. We chose intramolecular Michael reaction for the strategic bond formation because examination of molecular models of the hypothetical intermediate **3** showed that there are conformations in which the indicated carbon in the tetrahydropyridone ring is within easy bonding distance of the β carbon of the cyclohexenone ring. Furthermore, there is ample precedent for the formation of six-membered rings by both base- and acid-catalyzed intramolecular Michael reactions.



The synthesis started with the known keto acid **4**.[12] Treatment of **4** with oxalyl chloride in benzene provided the pseudo-acid chloride **5**, which was characterized as the crystalline hydroxy lactam **6**. The formation from 1,4-keto acids of pseudo-acid chlorides and hydroxy lactams is well precedented.[13] Alkylation of **6** with the bromo ketal **7**[14] provided **9** in poor yield. However, compound **9** was obtained in satisfactory yield by treatment of the pseudo-acid chloride **5** with the known amino ketal **8**.[15] The keto

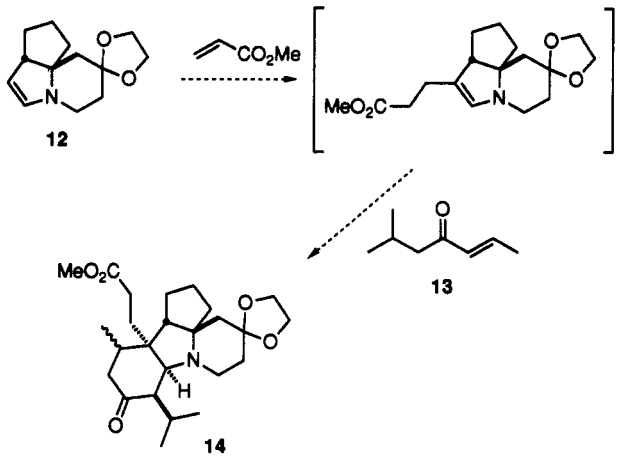


amide ring–chain tautomer of **9**, compound **10**, was obtained in better overall yield by treatment of keto acid **4** sequentially with triethylamine, ethyl chloroformate, and amino ketal **8**. Treatment of either **9** or **10** with catalytic amounts of *p*-toluenesulfonic acid in refluxing toluene provided the tricyclic ketal lactam **11** in excellent yield. The participation of a transient enol ether as the nucleophilic component in an intramolecular Mannich reaction, with formation of tetrahydropyridone ketal, was first observed by Wenkert and co-workers.[16] The overall yield of crystalline **11** was greater than 70% and the process was readily carried out on a multigram scale.

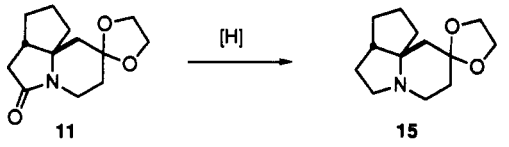


Our original intention was to convert lactam **11** into the endocyclic enamine **12**, which would be treated sequentially with methyl acrylate and enone **13** to form the tetracyclic keto lactam **14**. This plan was based on sound precedent, as Kuehne had demonstrated the reaction of an endocyclic enamine with methyl acrylate in 1966[17] and formation of cyclohexanone derivatives by the reactions of enamines and vinyl ketones is well known from Stork's pioneering work in the field.[18] However, this attractive

(9) A preliminary account has appeared: Heathcock, C. H.; Davidsen, S. K.; Mills, S.; Sanner, M. A. *J. Am. Chem. Soc.* **1986**, *108*, 5650.
(10) Corey, E. J.; Howe, W. J.; Orf, H. W.; Pensak, D. A.; Petersson, G. *J. Am. Chem. Soc.* **1975**, *97*, 6116.
(11) The supplementary material contains a detailed discussion of this analysis.
(12) (a) Linstead, R. P.; Meade, E. M. *J. Chem. Soc.* **1934**, 935. (b) Kötz, A. *Liebigs Ann. Chem.* **1933**, *55*, 1168.
(13) See inter alia: (a) Lutz, R. E.; Taylor, R. J. *J. Am. Chem. Soc.* **1933**, *55*, 1168. (b) Flitsch, W. *Chem. Ber.* **1970**, *103*, 3205. (c) Corey, E. J.; Williams, D. R. *Tetrahedron Lett.* **1977**, 3847.
(14) Williamson, L.; Schinz, H. *Helv. Chim. Acta* **1949**, *43*, 2152.
(15) Islam, A. M.; Raphael, R. A. *J. Chem. Soc.* **1955**, 3151.
(16) Wenkert, E.; Stevens, R. V.; Dave, K. G. *J. Am. Chem. Soc.* **1968**, *90*, 6177.
(17) Kuehne, M. E.; Bayha, C. *Tetrahedron Lett.* **1966**, 1311.

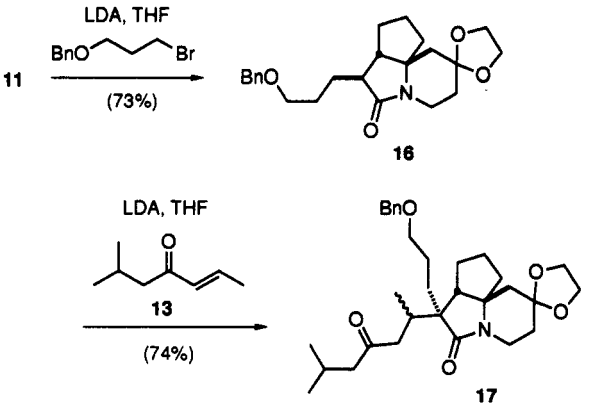


plan could not be put into practice because we were unable to prepare **12**. Numerous methods that have been used for the reduction of lactams to the carbinolamine or enamine oxidation level were evaluated (inter alia, diisobutylaluminum hydride,[19] lithium di- and triethoxyaluminum hydrides[20]) gave only mixtures of **11** and the fully reduced product, amino ketal **15**. The latter compound is, of course, also obtained in good yield by reduction of **11** with excess lithium aluminum hydride.

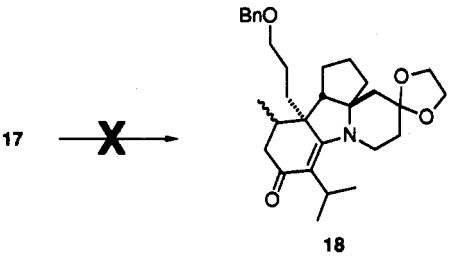


Having been thwarted in our attempts to introduce the propionic acid side chain by way of enamine **12**, we turned to alkylation of the lactam enolate. To this end, **11** was treated with LDA in THF and the resulting enolate alkylated with 3-(benzyloxy)-1-bromopropane[21] to obtain **16** as a single diastereomer. The stereochemistry suggested for **16** is based on the assumption that attack on the enolate of **11** occurs from the convex face of the bicyclo[3.3.0]octane unit. Lactam **16** was deprotonated and the resulting enolate treated with enone **13** to obtain adduct **17** as a 8:1 mixture of diastereomers at the methyl-bearing stereocenter. The stereochemistry of Michael adduct **17** and several related adducts was not determined. However, the observation of relatively high stereoselectivity in this reaction stimulated a more complete investigation of the stereochemistry of the Michael reactions of preformed lithium enolates; the results of the investigation have recently been published.[22]

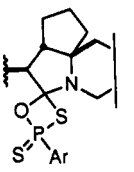
The easy acquisition of compound **17** (four steps from the known keto acid **4** and amino ketal **8**, 40% overall yield) was highly encouraging, since this intermediate contains the nitrogen and all of the carbon atoms of the methyl homodaphniphyllate skeleton. However, we were singularly unsuccessful in all attempts to bring about the cyclization of **17** to the required tetracyclic, vinylogous amide **18**. A variety of possible methods were investigated,



ranging from strongly basic (aluminum tri-*tert*-butoxide in refluxing toluene)[23] to a variety of reagents that might be expected to transform the lactam moiety of **17** into a more reactive haloimmonium ion (e.g., phosphorus trichloride, thionyl chloride, oxalyl chloride).[24]



16 was converted into the thioamide to provide a more reactive carbonyl group for the required cyclization. This conversion turned out to be rather difficult, both with P_4S_{10} and with Lawesson's P_4S_{10}–anisole reagent.[25] Consumption of lactam was slow, even under conditions of reflux. Furthermore, even when lactam was consumed, normal workup gave complex mixtures of products. These products seemed to be adducts of lactam and the Lawesson's reagent and may have structures such as shown below:[26]



The best procedure turned out to be reaction with Lawesson's reagent in THF with ultrasonication,[27] followed by treatment of the crude product mixture with methanolic KOH. Surprisingly, this treatment also resulted in replacement of one of the two dioxolane oxygens by sulfur; oxathiolane **19** was obtained in 46% yield, accompanied by 15% of the expected product, **20**. Thiation of the dioxolane was stereospecific, although it was not determined which of the diastereotopic oxygens was replaced. In order to obtain a homogeneous product, the crude product from the Lawesson's thiation was subjected to acidic workup and the resulting ketone reketalized in the normal manner;

(18) (a) Stork, G. A.; Brizzolara, A.; Landesman, H. K.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207. (b) Stork, G. A.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872.

(19) (a) Stevens, R. V.; Mehra, R.; Zimmerman, R. L. *J. Chem. Soc., Chem. Commun.* **1969**, 877. (b) Bohlmann, F.; Müllter, H.-J.; Schumann, D. *Chem. Ber.* **1973**, *106*, 3026.

(20) Rapoport, H.; Gless, R. D. *J. Org. Chem.* **1979**, *44*, 1324.

(21) Heathcock, C. H.; Kleinman, E. F.; Binkley, E. S. *J. Am. Chem. Soc.* **1982**, *104*, 1054.

(22) (a) Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132. (b) Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 152.

(23) (a) Hootelé, C.; Slosse, P. *Tetrahedron Lett.* **1979**, 4587. (b) Ban, Y.; Kimura, M.; Oishi, T. *Chem. Pharm. Bull.* **1976**, *24*, 1490.

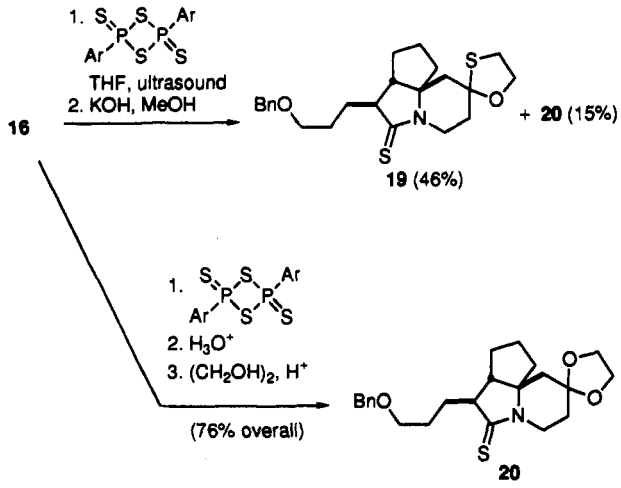
(24) For a detailed description of approximately two dozen different methods that were investigated, see: Sanner, M. A. Ph.D. Dissertation, University of California, Berkeley, 1983.

(25) (a) Lawesson, S.-O.; Shabana, R.; Scheibye, S.; Clausen, K.; Olesen, S. O. *Nouv. J. Chem.* **1980**, *4*, 47. (b) Lawesson, S.-O.; Thompson, I.; Clausen, K.; Scheibye, S. *Organic Syntheses*; Wiley: New York, 1990; Vol. 7, p 372.

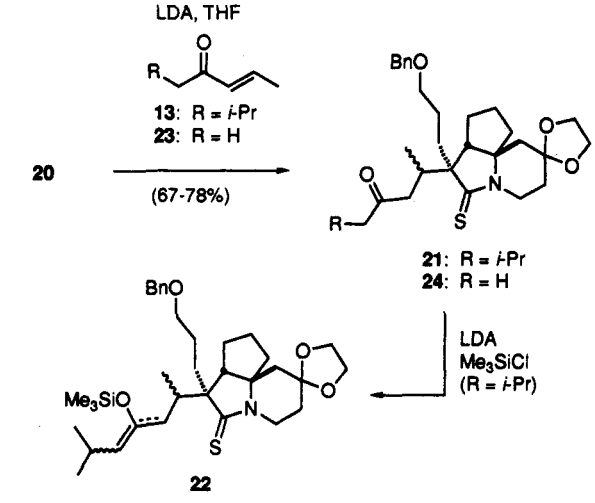
(26) Rauchfuss, T. B.; Zank, G. A. *Tetrahedron Lett.* **1986**, *27*, 3445.

(27) Raucher, S.; Klein, D. *J. Org. Chem.* **1981**, *46*, 3558.

thiolactam **20** was obtained in this way in 76% overall yield.



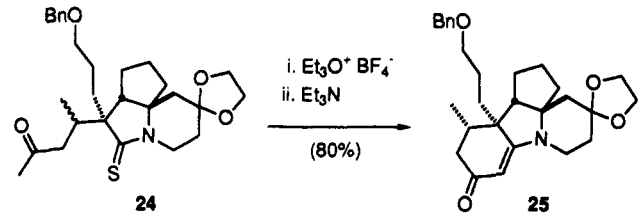
The lithium enolate of thiolactam **20** also reacted with enone **13** in reasonable yield and with high stereoselectivity (10:1). Again, however, we were not successful in bringing about closure to **18**. The silyl enol ether **22** was prepared by treatment of **21** sequentially with LDA and trimethylsilyl chloride. Although **22** reacted smoothly with Meerwein's salt,[28] the resulting ethylthioimmonium ion did not react further; upon aqueous workup, **21** was recovered.



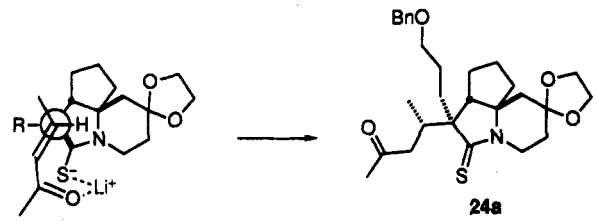
The most probable reason for the difficulty in cyclization of **17**, **21**, and their derivatives is steric hindrance of approach of a bulky enolate, enol, or enol ether to the relatively congested lactam, thiolactam, or immonium ion. This steric hindrance would be ameliorated if the isopropyl group were removed from the side chain. Since this group could, in principle, be installed at a later stage in the synthesis, we investigated Michael additions of amide **16** and thioamide **20** with pent-3-en-2-one (**23**). Reactions of the lithium enolate of **16** with **23** gave the desired Michael adduct in only low yield. The major products from the reaction were aldols resulting from 1,2-addition to the carbonyl group of **23**. Attempts to convert the initial aldolates to Michael adducts by longer reaction times at 0 °C or room temperature in the presence of HMPA led only to recovered **16** and polymeric materials. On the other hand, the lithium enolate of **20** reacted smoothly with **23** to give adducts **24** as a 83:17 mixture of diastereomers in about 80% yield.

(28) Meerwein, H. *Organic Syntheses*; Wiley: New York, 1973; Vol. 5, p 1080.

Treatment of a chloroform solution of **24** with triethyloxonium tetrafluoroborate gave a polar material (presumably the *S*-ethylthioimmonium salt) that was immediately treated with triethylamine. After refluxing for 1–3 days, the tetracyclic, vinylogous amide **25** was obtained in about 80% yield. Although **24** was a 5:1 mixture of

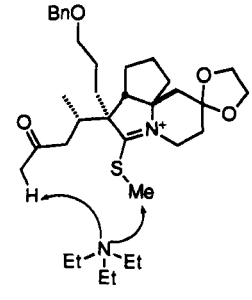


diastereomers at the methyl-bearing stereocenter, compound **25** was obtained as a single stereoisomer. Thus, the major diastereomer of **24** appears to undergo the cyclization significantly faster than the minor diastereomer. Although no definite proof has been adduced, we believe that the methyl-bearing stereocenters of the major Michael adduct and of **25** have the *S** relative configuration. This assignment is based on the fact that molecular models show that the transition state leading to cyclization of the isomer with the *R** relative configuration at this center suffers from nonbonded interactions between the methyl group and axial hydrogens in the piperidine ring. The *S** relative configuration would result from an eight-membered, chelated transition state in the Michael reaction, as has been suggested for other thioamide reactions:[21a]

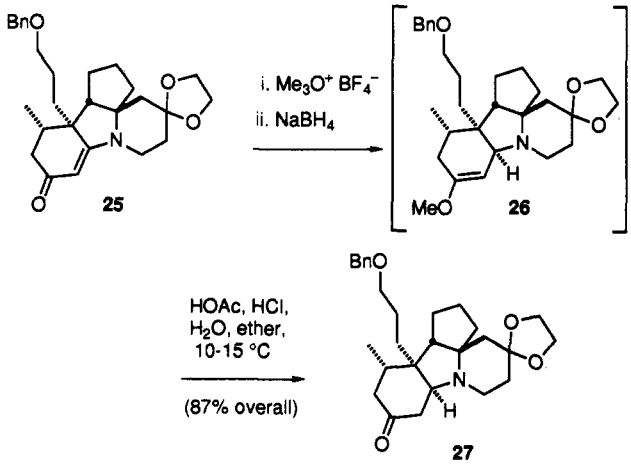


In the cyclization of **24** we observed that the use of 2,6-di-*tert*-butylpyridine (DBP) as a weakly basic, nonnucleophilic additive in the alkylation phase of the procedure markedly improves the reproducibility of the overall cyclization. This is presumably because $Et_3O^+BF_4^-$ is very hygroscopic and after a few uses outside a glovebox contains significant quantities of tetrafluoroboric acid. In the absence of DBP, the use of "old" $Et_3O^+BF_4^-$ leads to the destruction of **24** with formation of little **25**. Because DPB is very nonpolar, its presence in the reaction mixture does not complicate chromatographic purification of the product.

Attempts to use $Me_3O^+BF_4^-$ in the cyclization process were not very successful. Although the thiolactam is smoothly alkylated by this salt, the overall yield of **25** is only about one-half that obtained by the use of $Et_3O^+BF_4^-$. We think that the lower yields result from the fact that the methylthioimmonium ion undergoes a competing side reaction wherein the methyl group is transferred to triethylamine:

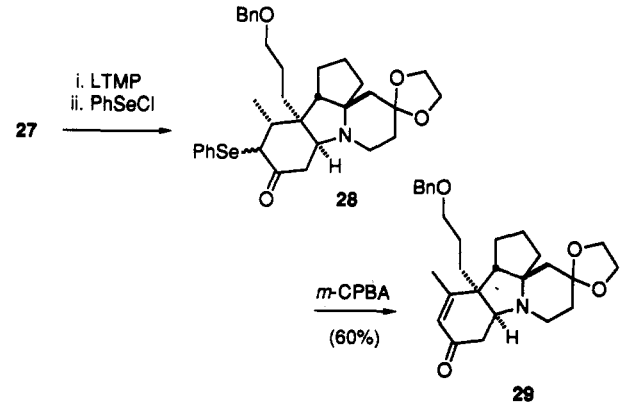


With the construction of the fourth ring finally secure, attention was focussed on the formal double-bond transposition that was required in order to generate an enone for the intramolecular Michael reaction that we planned to use to create the final ring. Vinylogous amide **25** was treated with $Me_3O^+BF_4^-$ in CH_2Cl_2 to obtain a salt that was reduced with methanolic $NaBH_4$ to afford the enol ether **26**. After mild hydrolytic workup, the saturated ketone **27** was obtained in excellent yield as a single diastereomer. The conditions of the hydrolysis step were crucial to the success of this transformation; if the hydrolysis medium was allowed to warm to room temperature, significant amounts of deketalized material were produced. The cis stereochemistry of the newly created ring juncture was suggested by the ^1H NMR spectrum of **26**. Specifically, the vinyl proton resonates as a doublet with δ 4.77 and J = 3.5 Hz. Decoupling experiments showed that the coupling was to the bridgehead proton (α to nitrogen) with δ 3.6. The observed coupling constant suggests a dihedral angle between the vinyl and bridgehead protons of 30° to 60°. With the indicated cis ring fusion, a number of conformations are possible, and a 30–60° dihedral angle is easily possible. However, the trans isomer is quite rigid with the dihedral angle between the vinyl and bridgehead protons being approximately 90°. Therefore, the trans isomer should show little or no coupling between these hydrogens. That this analysis was correct was shown by the ultimate conversion of **27** into methyl homodaphniphyllate.

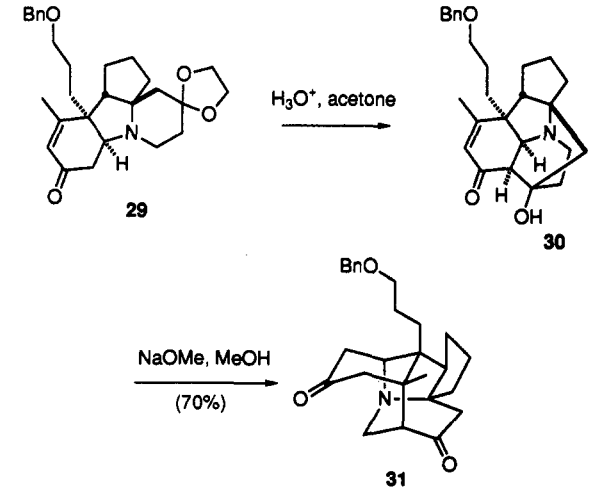


Deprotonation of **27** with lithium 2,2,6,6-tetramethylpiperidide (LTMP) in THF at −78 °C and treatment of the resulting enolate with benzeneselenyl chloride gave an unstable mixture of isomeric phenyl selenides (**28**) that was oxidized with 1 equiv of *m*-chloroperoxybenzoic acid; enone **29** was obtained in 60% overall yield. Silylation of the intermediate enolates gave a mixture of silyl enol ethers in a ratio of about 85:15. However, vinylogous amide **25** was not detected in the product mixture. Therefore, if the minor enolate was selenylated, the resulting selenoxide appears not to have undergone elimination.

With **29** in hand we had an opportunity for the first time to test the concept that the fifth ring of methyl homodaphniphyllate could be formed by an intramolecular Michael reaction. To this end, **29** was treated with HCl and H_2SO_4 in aqueous acetone to hydrolyze the ketal. The product of this treatment had clearly lost the ethylenedioxy group, but the absence of a saturated C=O and presence of an OH stretch in the infrared spectrum showed that it was not the expected saturated diketone. The most likely structure for this product is **30**, the intramolecular aldol addition product. This unexpected acid-catalyzed

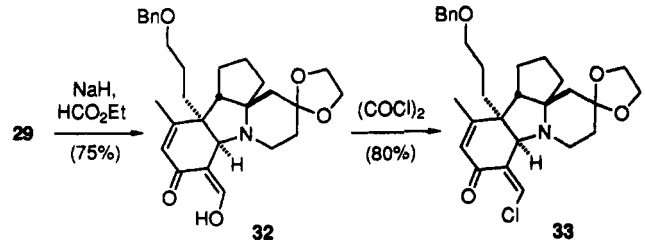


cyclization is of no particular concern, as the aldol cannot dehydrate for geometric reasons and it is well known that aldols are easily reversible under the basic conditions anticipated for the intramolecular Michael reaction. In the event, treatment of **30** with sodium methoxide in methanol led to smooth isomerization to the diketone **31**, possessing the full pentacyclic skeleton of daphniphylline and methyl homodaphniphyllate. Compound **31** was obtained in 70% overall yield for the two steps. The structure of **31** was assigned on the basis of its infrared spectrum and extensive NMR spectra, including ^{13}C NMR and ^1H NMR spectra and a 500-MHz COSY spectrum which permitted assignment of most of the ^1H NMR resonances. Because **31** has two quaternary centers, a nitrogen, and two carbonyl groups, its ^1H NMR spectrum is fairly simple. The protons in the two carbonyl-containing rings appear as two AB patterns and two ABX patterns.

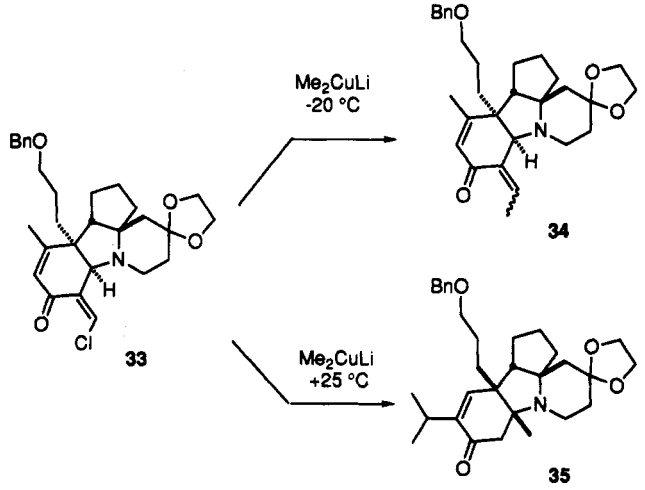


Although compound **31** has the desired skeleton, we thought it unlikely that the necessary isopropyl group could be installed selectively at the proper site. However, in intermediate **29** there is only one enolizable site. Therefore, we concentrated our efforts on this compound. Treatment of **29** with NaH in ethyl formate produced the highly polar, blue-fluorescent α-hydroxymethylene derivative **32** in 72–78% yield. When **32** was treated with exactly 1 equiv of oxalyl chloride in chloroform at room temperature, a rapid reaction occurred to form the hydrochloride salt of chloro enone **33**. Neutralization of this salt gave **33**, accompanied by 5–10% of **32**, the total yield of neutral material being about 80%. Because of its sensitivity to chromatography, **33** was generally used without purification.

Treatment of α-chloro enone **33** with lithium dimethylcopper at temperatures below −20 °C provided enone **34** in about 70% yield as a mixture of geometric isomers about the double bond. When the cuprate reaction

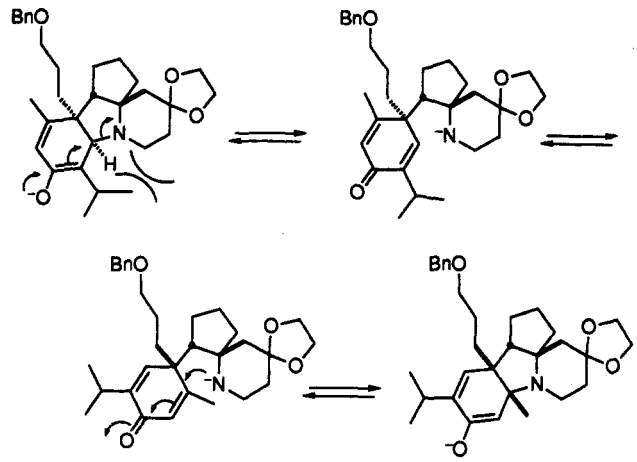


was conducted at room temperature, a monounsaturated ketone having an isopropyl group was produced. However, examination of the ^1H NMR spectrum of this material showed that it was not the expected product of addition of methyl to the exocyclic double bond of **34**. First, the methyl group appears as a singlet with δ 1.12, rather than the expected δ 1.5–1.8. Second, the vinyl resonance appeared at δ 6.22, whereas in related structures in this series it had always appeared in the neighborhood of δ 5.8. Third, there was a distinct AB pattern with δ = 2.35 and 2.59 and J = 16.0, characteristic of a CH_2 group adjacent to a carbonyl group. Finally, decoupling experiments showed that the isopropyl methine resonates at about δ 2.85, consistent with it being allylic. Furthermore, the isopropyl methine is also weakly coupled to the vinyl proton. On the basis of these data, structure **35** was assigned to the dimethylation product.

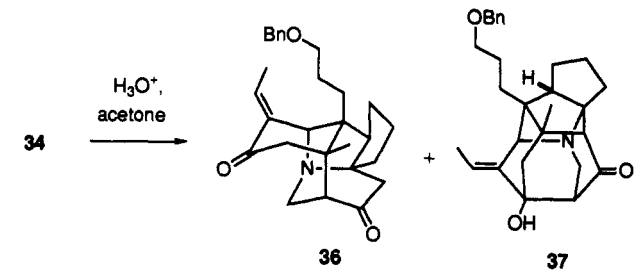


The probable mechanism for the formation of **35** is shown below. It is proposed that the enolate resulting from conjugate addition to **34** undergoes β elimination of the pyrrolidine nitrogen, giving a 4,4-disubstituted cyclohexadienone intermediate. Addition of the amide nitrogen to the other enone provides the enolate ion of **35**. The two enolate ions are presumably in equilibrium. The driving force favoring the ion corresponding to **35** is presumably relief of the indicated interaction, which is very much like having isopropyl and methyl groups 1,3-diaxial in a cyclohexane ring.

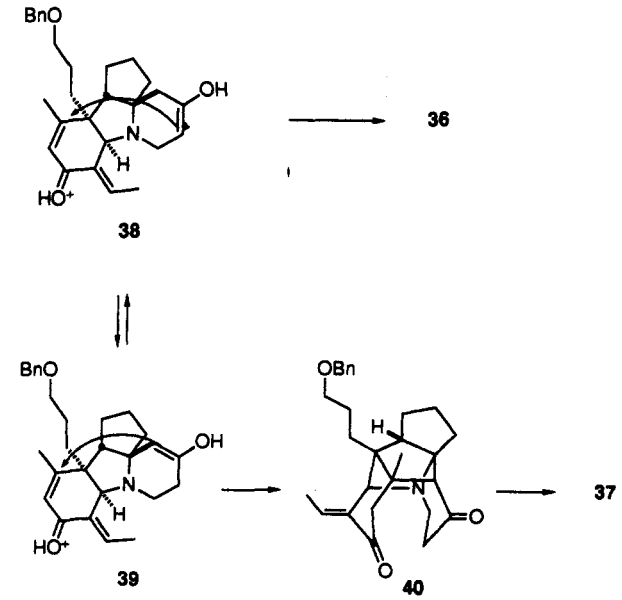
The ease of the foregoing skeletal rearrangement did not bode well for further efforts to install the isopropyl group at this juncture in the synthesis; even if a method was found, the strongly acidic conditions of the ketal hydrolysis step would provide ample opportunity for a similar isomerization. However, we noted that in enone **34** such a rearrangement is not possible, since the ketone is blocked by the ethylidene group from the enolization leading to its destruction. Therefore, **34** was treated with a mixture of HCl and H_2SO_4 in aqueous acetone. Over a period of 2 days at room temperature, two more polar compounds were formed in a ratio of about 3:1. The NMR spectra of the major isomer were in full agreement with the expected



Michael cyclization product **36**. The *E* configuration of the enone double bond was inferred from the extreme downfield shift of the vinyl proton (δ 7.33). The ^{13}C NMR spectrum of the minor product showed only one carbonyl signal and had an unusual resonance at δ 87.6, consistent with a quaternary carbon joined to oxygen. Finally, the solution infrared spectrum of the minor product showed typical tertiary alcohol absorptions at 3600 and 3400 cm^{-1}. This minor byproduct is therefore believed to be the hexacyclic aldol **37**.

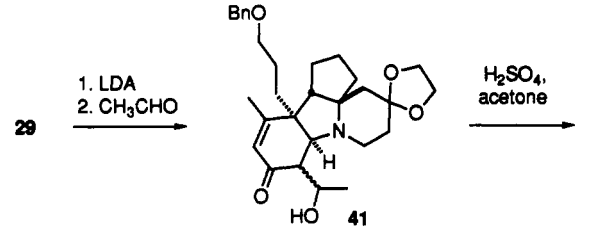


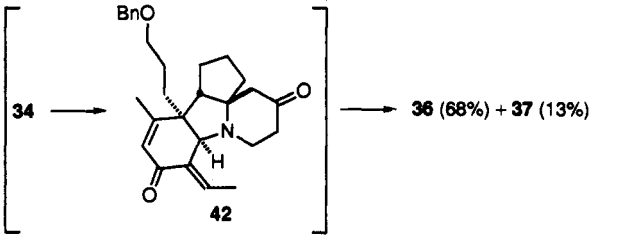
A proposed mechanism for the formation of **36** and **37** is summarized below. The major product is presumed to come from acid-catalyzed Michael reaction of enol **38**. The isomeric enol **39** would lead to diketone **40**, which should undergo rapid aldolization. Attempts to isomerize **37** to **36** by treatment with base were not successful.



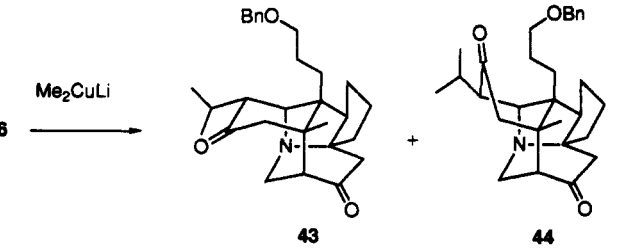
Examination of the successful route to **36** suggested that a considerable simplification was possible. To this end, ketone **29** was treated with a THF solution of LDA from

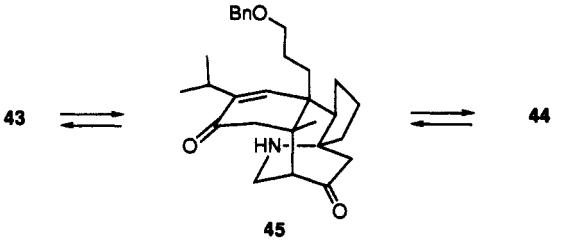
which all of the hexane had been removed under vacuum. The resulting enolate was treated with acetaldehyde to give a mixture of aldols **41** in virtually quantitative yield. The crude aldol product was dissolved in acetone and treated with about 25 molar equiv of concentrated H_2SO_4. The resulting solution was stirred at room temperature while being monitored by TLC. This analysis showed that dehydration of the β hydroxy ketone occurred immediately, leading to a mixture of the diastereomers of enone **34**. A new material, shown by its NMR spectra to be **42**, was formed as the isomers of **34** slowly disappeared. Dione **36** and aldol **37** appeared more slowly than **42**, which accumulated until it comprised about one-half of the total product mixture. Toward the end of the reaction, highly polar byproducts began to appear, so it was normally monitored closely by TLC and worked up when **42** had disappeared. In this manner, dione **36** was obtained in 68% yield, accompanied by 13% of **37**.



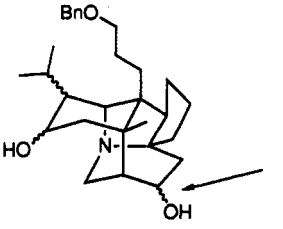


With a satisfactory route to **36** in hand, efforts were directed to introduction of the final carbon of methyl homodaphniphyllate. We had planned to accomplish this task by conjugate addition of lithium dimethylcopper and had anticipated no problems with the maneuver since the isopropyl group in the natural product occupies an equatorial position. However, this proved to be overly optimistic. Although **36** reacted smoothly with lithium dimethylcopper, the product was a mixture of diones, assigned structures **43** and **44**. Separation of the isomers from one another was complicated by the fact that they equilibrate fairly easily upon contact with silica gel. Thus, when the mixture was analyzed by TLC, two spots were seen. If the plate was allowed to stand for 5 min and then developed in the perpendicular direction, two clear off-diagonal spots, whose mobilities were the same as the two original spots, were seen. Attempts to separate the two isomers on a silica gel column with a suitable solvent system (3% methanol in chloroform) failed, even though their TLC mobilities are quite different. The unexpectedly easy equilibration of **43** and **44** is probably related to the facile rearrangement we had observed earlier in the reaction of **33** and **34** with lithium dimethylcopper. In the case of **43** the nitrogen is β to the carbonyl group and held rigidly axial. Acid-promoted β elimination would give **45**, which could reclose to give either **43** or **44**.





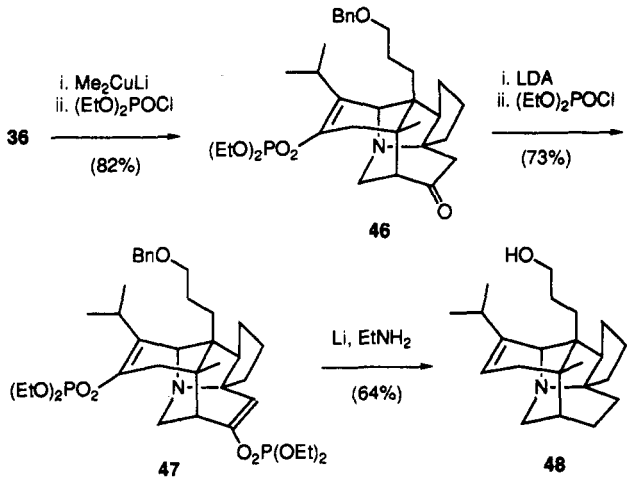
Although stereoisomer **44** had been ignored in our planning, post facto modelling by molecular mechanics showed the two ring systems to be rather close in energy. Although these calculations suggested that the desired isomer, **43**, should predominate slightly in the equilibrium, we had no method at the time to tell which isomer was major. Furthermore, attempts to deoxygenate the mixture of **43** and **44** were unsuccessful. Conventional Wolff–Kishner conditions led to extensive decomposition. Furthermore, although the mixture reacted with (*p*-toluenesulfonyl)hydrazine to give a monohydrazone, the more hindered carbonyl group failed to react. The mixture was reduced in high yield by lithium aluminum hydride, but the resulting mixture of highly polar stereoisomeric amino diols could not be purified by chromatography or converted into suitable derivatives. For example, acylation reactions seemed to occur on only one of the two hydroxy groups, presumably the less hindered one as shown in the following structure:



Although the amino diols were available in reasonable yield, they did not constitute viable synthetic intermediates. First, at this point we were dealing with a large number of diastereomeric products and were not even sure of the relative stereochemistry at the important isopropyl-bearing center, which was no longer under control. Second, all of the reactions we had attempted on the amino diones or the amino diols suggested that one position (carbonyl or secondary alcohol) was exceedingly hindered. For these reasons, we abandoned further work with the **43**/**44** mixture.

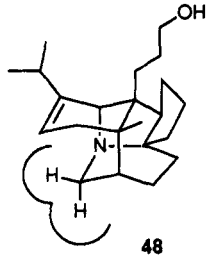
As an alternative method for removing the unwanted carbonyl groups, the enolate resulting from the lithium dimethylcopper conjugate addition was trapped with diethyl phosphochloridate to obtain the enol phosphate **46**. Sequential treatment of this material with LDA and diethyl phosphorochloridate provided the bis(enol phosphate) **47**. Reduction of the latter derivative with lithium in ethylamine (Ireland method)[29] afforded the unsaturated amino alcohol **48**. Reductive cleavage of the vinyl phosphate groups and benzyl ether were expected in this reduction. Although saturation of one of the two isolated double bonds was something of a surprise, there is precedent for reduction of strained double bonds under these conditions.[30]

(29) Ireland, R. E.; Pfister, G. *Tetrahedron Lett.* **1969**, 2145.



46 47 48

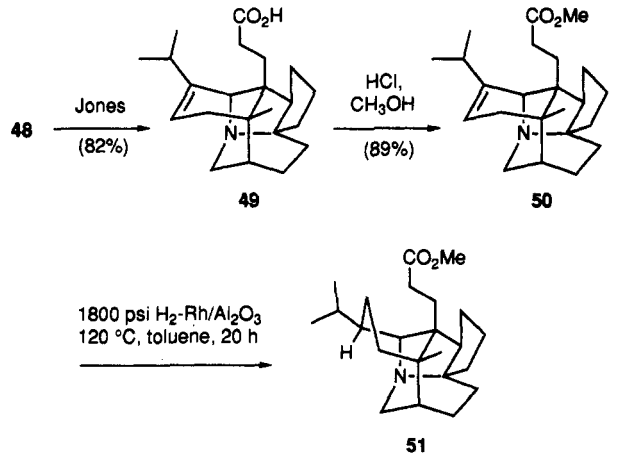
At this juncture, the total synthesis of methyl homodaphniphyllate appeared to be well in hand. With the two oxygens out of the way, it remained only to hydrogenate the remaining double bond and adjust the oxidation state of the three-carbon side chain. We had assumed that stereoselective hydrogenation of the double bond would present no difficulty, as molecular models indicated that the bottom face is severely hindered by the indicated methylene group:



48

In addition, there appeared to be the possibility of using the hydroxypropyl group to direct hydrogenation from the top face of the double bond. Preliminary experiments showed that **48** was very resistant to hydrogenation. The compound was completely inert at room temperature and atmospheric pressure with all catalysts evaluated. Similarly, it was not affected by attempted hydrogenation over Raney nickel, copper chromite, iridium on carbon, Adams' catalyst, or platinum on carbon in methanol at temperatures from 60 °C to 160 °C and pressures of 800 psi up to 1600 psi.[31] Our first success was achieved by the use of rhodium on alumina in ethanol at 120 °C and 1800 psi for 20 h. Under these conditions, a single hydrogenation product was produced in 85% yield. Encouraged by this apparent success, we oxidized amino alcohol **48** to amino acid **49**, which was esterified to obtain methyl dehydrohomodaphniphyllate (**50**). Hydrogenation of **50** under the previously developed conditions (except that toluene was used as solvent instead of ethanol) gave a single isomer in 82% yield.

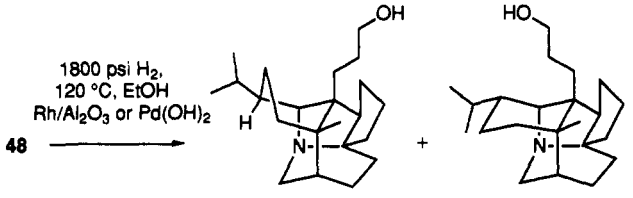
However, comparison of the high-field ^{1}H NMR spectrum of the hydrogenation product with that of an authentic sample of natural methyl homodaphniphyllate, kindly supplied by Professors Y. Hirata and S. Yamamura, showed that the hydrogenation product was *not* identical



49 50

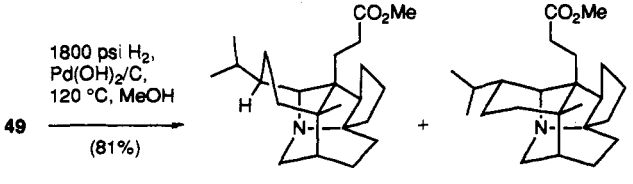
51

with the natural product. Surprisingly, the hydrogenation had provided **51**, the diastereomer of methyl homodaphniphyllate! In retrospect, we also can surmise that the hydrogenation of **48** under the influence of rhodium had presumably afforded **52**, rather than **53**. This unexpected stereochemical outcome probably results from isomerization of the double bond to a more readily hydrogenated position in which the bottom face of the double bond is actually less hindered than the top face.



52 53

At this juncture in the synthesis, we investigated the possible use of a cationic rhodium catalyst that had been used by Evans and Morrissey for the stereodirected hydrogenation of allylic and homoallylic alcohols.[32] However, this method was also ineffective for reduction of **48**; various trials led only to recovered starting material or decomposition of the catalyst. Partial success was finally achieved when it was found that **48** was reduced by hydrogen in the presence of Pearlman's catalyst, $Pd(OH)_2$,[33] in ethanol at 120 °C and 1800 psi hydrogen pressure for 20 h. Under these conditions, a 1:1 mixture of **52** and an isomeric alcohol, presumably **53**, were formed in 87% yield. Hydrogenation of amino acid **49** over Pearlman's catalyst provided a 1:1 mixture of **51** and racemic methyl homodaphniphyllate ((±)-**2**) in 81% yield. It is noteworthy that the methyl ester was formed under the conditions of the hydrogenation reaction. The two isomers were separated by careful chromatography on silica gel and the new isomer was shown to be identical by 500-MHz ^{1}H NMR spectroscopy with an authentic sample.



51 2

(30) Kaiser, E. M. *Synthesis* **1972**, 391.
(31) We experienced considerable technical difficulties in these exploratory experiments because of the need to carry out the reactions at high temperature and high pressure on a milligram scale. They were successfully carried out with the use of a 45-mL Parr high-pressure hydrogenation bomb equipped with a gauge block assembly and gas inlet port. We thank Professor R. G. Bergman for the loan of this apparatus.
(32) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866.
(33) Pearlman, W. M. *Tetrahedron Lett.* **1967**, 1633. The catalyst used was obtained from the Aldrich Chemical Company, catalog no. 21,291-1.

With the isolation of (±)-2 from the foregoing hydrogenation, the first total synthesis of a *Daphniphyllum* alkaloid had been achieved. Starting with keto acid 4, the synthesis required 15 steps and proceeded in about 1.1% overall yield. It was marred by a complete lack of stereocontrol at the isopropyl-bearing stereocenter. However, the synthesis provided us with invaluable experience in dealing with the daphniphylline skeleton. The experience taught us an important lesson about applying logical skeletal analysis without a corresponding attention to the natural functionality of the target molecule. In the present case, for example, network analysis led us more-or-less smoothly to the daphniphylline skeleton (e.g., diketone 31). However, we had not anticipated the difficulty that we would encounter in removal of the two carbonyl groups that were built into the synthetic design in order that the strategic bond could be formed. In the end, it was the removal of this activating functionality that proved to be the major flaw in an otherwise acceptable synthesis, as we were unable to solve the problem of the stereochemistry of the only stereocenter where control was really an issue. Largely as a result of these difficulties, and simultaneous with the concluding phases of the synthesis that is described in this paper, we embarked on a totally different approach to the *Daphniphyllum* alkaloids. This new approach is described in the succeeding papers.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF), ethyl ether, and 1,2-dimethoxyethane (DME) were distilled from sodium/benzophenone immediately prior to use. Diisopropylamine and triethylamine were distilled from CaH_2 and stored over 3-Å Linde molecular sieves. Hexamethylphosphoric triamide (HMPA) was distilled from CaH_2 at reduced pressure (15 Torr) and stored over Linde 4-Å molecular sieves. All reactions involving organometallic reagents were conducted under a N_2 atmosphere. Evaporation of solvents was accomplished with a rotary evaporator. Boiling points and melting points (Pyrex capillary) are uncorrected. IR spectra were determined as films on NaCl plates unless otherwise indicated. ^1H NMR and ^{13}C NMR spectra were determined as $CDCl_3$ solutions, unless otherwise indicated. J values are in hertz. Chemical shifts are expressed in ppm downfield from internal tetramethysilane. Mass spectral data are tabulated either as m/z (intensity expressed as percent of total ion current) or (percent of base peak). A Bransonic 220 ultrasonic cleaner was used for ultrasonic irradiation. Preparative gas–liquid partition chromatography (GLC) was done with a Varian Aerograph 920 gas chromatograph equipped with a thermal conductivity detector using helium as carrier gas (60 mL/min) and a 10 ft × $^1/_4$ in. stainless steel, 8% SE-30 column (column A) or a 6 ft × $^1/_4$ in. stainless steel, 20% SE-30 column (column B).

2-Methyl-1,3-dioxolane-2-ethanamine (8). To a suspension of 215 g (0.822 mol) of 2-methyl-2-(2-phthalimidoethyl)-1,3-dioxolane[15] in 1000 mL of absolute methanol (from a fresh bottle of reagent-grade solvent) was added 40.0 mL (0.822 mol) of hydrazine hydrate (99–100%). The mixture was protected from atmospheric moisture with a drying tube and heated to reflux. Solution was achieved after several minutes of boiling, and a white precipitate began to form within 30 min. After 4 h of reflux, the mixture was cooled to room temperature. A solution of 65 g (1 mol) of KOH in 150 mL of absolute methanol was added to the reaction vessel with mechanical stirring. The voluminous, white precipitate was filtered through Celite. Most of the methanol was removed by distillation at ambient pressure through a 24-cm column packed with glass helices. The residue was filtered again and washed with a minimal amount of methanol. The filtrate was fractionally distilled through a 22-cm silvered, vacuum-jacketed column packed with glass helices. Methanol and water were removed at 30–50 °C (140–150 Torr) and 74.0 g (69%) of amine 8 was collected at 76 °C (11–12 Torr) as a colorless oil. ^1H NMR (250 MHz): δ 1.16 (s, 2), 1.28 (s, 3), 1.73 (t, 2, J = 7), 2.70 (t, 2, J = 7), 3.85 (s, 4). Anal. Calcd for $C_6H_{13}NO_2$: C, 54.99; H, 9.95; N, 10.68. Found: C, 54.93; H, 10.05; N, 10.63.

***N*-[2-(2-Methyl-1,3-dioxolan-2-yl)ethyl]-2-oxocyclopentaneacetamide (10).** A 2-L, four-necked, round-bottomed flask was fitted with a mechanical stirrer, a thermometer, and a gas inlet. The flask was flushed with N_2 and sealed with a rubber septum. The reaction vessel was charged with 600 mL of THF and 27.4 mL (0.287 mol) of ethyl chloroformate (freshly distilled from $CaCO_3$). Stirring was commenced and the flask was cooled to −30 °C with a $CaCl_2$–water–dry ice slush bath (45 g of $CaCl_2 \cdot 2H_2O$ per 100 mL of water or 1 pound $CaCl_2 \cdot 2H_2O$ per 1000 mL of water). A THF solution (175 mL) of keto acid 4[12] (40.8 g, 0.287 mol) and triethylamine (40.0 mL, 0.287 mol) was prepared in a 500-mL Erlenmeyer flask fitted with a rubber septum. The acid–amine solution was chilled to −78 °C and added to the −30 °C ethyl chloroformate solution with a stainless steel cannula. With only one N_2 source available, this transfer was best accomplished by temporarily replacing the gas inlet with a drying tube and then gently pressurizing the Erlenmeyer flask with N_2 to allow the acid solution to flow into the reaction vessel. The rate of addition was regulated so that the temperature of the reaction mixture never exceeded −26 °C. The total time for the addition was approximately 30 min. The resulting white suspension was allowed to stir for an additional 2 h at −30 °C. Under generous N_2 flow, the rubber septum was replaced by a 50-mL dropping funnel containing 37.6 g (0.287 mol) of amine 8. The amine was allowed to flow rapidly into the reaction flask (less than 5 min for the addition), during which time the temperature rose to −10 °C. The reaction mixture was allowed to warm to room temperature overnight.

The reaction mixture was diluted with 200 mL of water and 100 mL of ethyl acetate, the contents of the flask were transferred to a separatory funnel, the layers were separated, and the aqueous phase was extracted two times with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered, an evaporated to obtain an oily residue that crystallized after removal of residual solvent in vacuo. The crude product (75.6 g, 103%) was dissolved in 250 mL of CH_2Cl_2 and washed with saturated $NaHCO_3$ (2 × 100 mL) and brine (1 × 100 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated to give 65.4 g (89%) of crystalline 10. An analytical sample, mp 64–65 °C, was prepared by recrystallization from ether–petroleum ether. IR ($CHCl_3$): 3420, 1730, 1660 cm^{-1}. ^1H NMR (250 MHz): δ 1.35 (s, 3), 1.4–2.7 (m, 8), 1.80 (t, 2, J = 6), 3.27 (q, 2, J = 6), 3.85 (s, 4), 6.5 (br s, 1). ^{13}C NMR (50 MHz): δ 20.4, 23.5, 29.4, 35.0, 36.0, 37.3, 37.6, 46.1, 64.4, 109.5, 170.7, 219.7. Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.15; H, 8.29; N, 5.49. Found: C, 61.14; H, 8.21; N, 5.39.

(7a*R,10a*S**)-(±)-Hexahydrospiro[cyclopent[*i*]indolizine-2(1*H*),2'-[1,3]dioxolan]-6(7*H*)-one (11).** A solution of 31.5 g (0.123 mol) of 10 and 1 g (0.005 mol) of *p*-toluenesulfonic acid monohydrate in 150 mL of toluene was heated at reflux under a Dean–Stark water separator for 18 h. The solution was cooled to room temperature and the solvent was removed with a rotary evaporator. The residue was taken up in 200 mL of CH_2Cl_2 and washed with saturated $NaHCO_3$ solution (2 × 50 mL) and brine (1 × 50 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated to a brown oil. Distillation at 150 °C (0.001 Torr) with a Kugelrohr apparatus gave 24.2 g (83%) of a nearly colorless oil that slowly crystallized when seeded. An analytical sample, mp 69–70 °C, was obtained by recrystallization from di-*n*-butyl ether (washing with cold di-*n*-butyl ether and pentane). IR ($CHCl_3$): 1665 cm^{-1}. ^1H NMR (250 MHz): δ 1.35–2.05 (m, 10), 2.12 (dd, 1, J = 17.6, 4.6), 2.30 (m, 1), 2.72 (dd, 1, J = 17.6, 10.4), 2.87 (ddd, 1, J = 13, 13, 3.5), 3.96 (m, 4), 4.16 (ddd, 1, J = 13.4, 5.4, 1.8). ^{13}C NMR (d_6-acetone): δ 25.3, 34.4, 34.9, 35.4, 37.1, 38.1, 42.8, 45.6, 64.5, 65.3, 71.2, 108.2, 172.7. Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.99; H, 8.12; N, 5.85.

(7a*R,10a*S**)-(±)-Hexahydrospiro[cyclopent[*i*]indolizine-2(1*H*),2'-[1,3]dioxolane] (15).** To a solution of 0.254 g (1.07 mmol) of 11 in 5 mL of THF was added 0.572 mL (1.07 mmol) of a 1.87 M solution of $LiAlH_4$ in THF. The reaction mixture was heated at reflux for 2 h, cooled to room temperature, and carefully quenched with a few drops of water. After adding another 10 mL of water and 0.2 g of solid NaOH, the mixture was extracted with ether (3×). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give 0.203 g (85%) of a

colorless oil. An analytical sample was obtained by preparative GLC (column A, 210 °C). ^{1}H NMR (250 MHz): δ 1.1–2.2 (m, 13), 2.5–3.05 (m, 4), 3.83 (s, 4). ^{13}C NMR (50 MHz): δ 25.8, 29.3, 31.6, 33.4, 36.3, 40.1, 43.3, 50.7, 51.4, 63.4, 64.3, 71.6, 108.5. Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.78; H, 9.31; N, 6.25.

(7*R,7a*R**,10a*S**)-(±)-Hexahydro-7-[3-(phenylmethoxy)propyl]spiro[cyclopent[*i*]indolizine-2(1*H*),2′-[1,3]dioxolan]-6(7*H*)-one (16).** Diisopropylamine (2.40 mL, 17.1 mmol) in 12 mL of THF at 0 °C was treated with 11.4 mL of *n*-butyllithium (17.1 mmol; 1.5 M in hexane) for 15 min. Lactam **11** (2.71 g, 11.4 mmol) was added as a solution in 7 mL of THF. Stirring was continued for 1 h and 3.92 g (17.1 mmol) of 3-(benzyloxy)-1-bromopropane[21] was added. The reaction mixture was allowed to reach room temperature overnight and was then quenched with 20 mL of saturated NH_4Cl. The mixture was extracted with ethyl acetate (3 × 40 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give a brown oily residue. Excess bromide was removed by distillation with a Kugelrohr apparatus (175 °C ot, 0.005 Torr). After changing receiver bulbs, the residue was distilled at 180 °C (ot) and mercury diffusion pump pressure (<0.005 Torr) to give 3.23 g (73%) of lactam **16**. An analytical sample was prepared by flash silica gel chromatography with 1:1 hexane–ethyl acetate as eluant. IR (film) 1670 cm^{-1}. ^{1}H NMR (250 MHz): δ 1.4–2.2 (m, 16), 2.86 (dt, 1, *J* = 2.5, 13), 3.49 (dt, 2, *J* = 1.5, 6.4), 3.95 (m, 4), 4.16 (ddd, 1, *J* = 13.4, 5.4, 1.6), 4.50 (s, 2), 7.35 (s, 5). ^{13}C NMR (50 MHz): δ 24.5, 27.0, 29.3, 33.3, 33.9, 34.8, 36.1, 46.1, 49.1, 49.2, 63.5, 64.3, 68.8, 69.7, 72.5, 107.1, 127.0, 127.1, 127.8, 138.1, 174.0. M^+ calcd for $C_{23}H_{31}NO_4$: 385.2253. Found: 385.2251. Anal. Calcd for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.11; N, 3.63. Found: C, 71.39; H, 8.06; N, 3.62.

(1″*R*+*S*,7*R,7a*R**,10a*S**)-(±)-Hexahydro-7-(1″,5″-dimethyl-3″-oxohexyl)-7-[3-(phenylmethoxy)propyl]spiro[cyclopent[*i*]indolizine-2(1*H*),2′-[1,3]dioxolan]-6(7*H*)-one (17).** To a solution of 0.454 mL (3.24 mmol) of diisopropylamine in 1.6 mL of THF at 0 °C was added 2.59 mL (3.24 mmol) of *n*-butyllithium in hexane. The resulting solution was stirred for 15 min and 0.569 g (1.48 mmol) of lactam **16** in 2 mL of THF was added dropwise. The solution was allowed to stir for 2 h and 0.449 g (3.56 mmol) of 6-methyl-2-hepten-4-one (**13**)[34] was then added all at once. After 1.5 min, the reaction was quenched with saturated NH_4Cl and water and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water (2 × 10 mL) and brine (1 × 10 mL), dried ($MgSO_4$), filtered, and evaporated to leave 0.870 g of a yellow oil. Purification by column chromatography on 45 g of silica gel with 60:40 hexane–ethyl acetate gave 0.558 g (74%) of a colorless oil. IR ($CHCl_3$): 1701, 1660 cm^{-1}. ^{1}H NMR (250 MHz): δ 0.82 (d, 3, *J* = 6.6), 0.88 (d, 3, *J* = 6.5), 0.90 (d, 3, *J* = 6.5), 1.40–2.35 (m, 20), 2.48 (m, 1), 2.85 (dt, 1, *J* = 3.1, 13.1), 3.44 (bt, 2, *J* = 6), 3.97 (m, 4), 4.15 (m, 1), 4.48 (s, 2), 7.26 (s, 5). ^{13}C NMR (50 MHz): δ 13.9, 22.3, 22.4, 24.3, 24.7, 25.9, 26.7, 30.1, 33.3, 34.3, 35.1, 36.3, 45.3, 47.2, 49.4, 51.4, 52.0, 63.6, 64.5, 67.9, 70.6, 72.5, 107.5, 127.3, 128.0, 138.6, 175.1, 209.2. Anal. Calcd for $C_{31}H_{45}NO_5$: C, 72.76; H, 8.86; N, 2.74. Found: C, 72.49; H, 8.77; N, 2.64.

(7*R,7a*R**,10a*S**)-(±)-Hexahydro-7-[3-(phenylmethoxy)propyl]spiro[cyclopent[*i*]indolizine-2(1*H*),2′-[1,3]thioxolane]-6(7*H*)-thione (19).** To a solution of 0.622 g (1.72 mmol) of lactam **16** in 10 mL of THF was added 1.00 g (2.48 mmol) of Lawesson's reagent[25] under a N_2 atmosphere. The reaction flask was suspended in an ultrasonic water bath for 13.5 h. Irradiation was stopped and methanolic KOH (0.75 g in 10 mL methanol) was added. After 1.5 h of stirring at room temperature, the solution was diluted with water (25 mL) and ether (25 mL), the layers were separated, and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give 0.654 g of a yellow oil. Purification by column chromatography on 29 g of silica gel with 4:1 hexane–ethyl acetate gave 0.104 g (15%) of dioxolane thiolactam **20** and 0.319 g (46%) of oxathiolane thiolactam **19**. An analytical sample was prepared by preparative TLC (silica gel) with the same solvent system. ^{1}H NMR (250 MHz): δ 1.4–2.4 (m, 15), 2.55 (m, 1), 3.09 (d, 2, *J* = 5.9), 3.28 (bt, 1, *J* = 13), 3.52 (m, 2), 4.20 (d, 1, *J* = 5.9), 4.51 (s, 2), 4.90 (ddd, 1, *J* = 1.8, 5.0, 13), 7.33 (br s, 5). ^{13}C NMR (50 MHz): δ 24.9, 26.9, 32.2, 33.3, 33.6, 37.2, 37.9, 40.6, 50.2, 50.6, 60.1, 70.1, 70.5, 72.8, 78.3, 91.5, 127.3, 127.5, 128.1, 138.2, 202.1. Anal. Calcd for $C_{23}H_{31}NO_2$: C, 66.15; H, 7.48; N, 3.35. Found: C, 65.76; H, 7.49; N, 3.24.

(7*R,7a*R**,10a*S**)-(±)-Hexahydro-7-[3-(phenylmethoxy)propyl]spiro[cyclopent[*i*]indolizine-2(1*H*),2′-[1,3]dioxolane]-6(7*H*)-thione (20).** Lactam **16** (7.004 g, 18.2 mmol) was placed in a dry, 250-mL flask, degassed with heating under high vacuum, blanketed with N_2, and dissolved in 250 mL of THF. Lawesson's reagent (15.9 g, 39.3 mmol) was added under a stream of N_2 and the flask was placed in an ultrasonic bath filled with an ice–water mixture. The temperature was allowed to come to ambient temperature over 1.5 h. After a total of 8 h, during which the flask was occasionally swirled by hand, the reaction mixture was poured into 250 mL of 10% NaOH, stirred briefly, and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to give 15.0 g of a dark yellow oil. This residue was filtered through 180 g of silica gel with 50:50 hexane/ethyl acetate to give 7.7 g of a thick red oil. This oil was dissolved in a mixture of 50 mL of methanol, 25 mL of acetone, and 9 mL of 1 M HCl, and the reaction mixture was stirred at room temperature for 45 min. The solution was then made basic with K_2CO_3 and most of the solvent was removed at room temperature. The residue was treated with water and extracted with ether (2 × 50 mL) and $CHCl_3$ (2 × 50 mL). The combined organic extracts were dried (Mg_2SO_4) and concentrated to give 6.27 g of a yellow oil. This oil was dissolved in 125 mL of benzene, treated with 9.0 mL of ethylene glycol and 1.0 g of pyridinium *p*-toluenesulfonate, and heated at reflux under a Dean–Stark trap. After 7 h, the mixture was cooled and most of the solvent was removed. The residue was treated with saturated $NaHCO_3$ and the aqueous phase was extracted with ethyl acetate (4 × 40 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated to give 6.29 g of a cloudy yellow oil. This oil was purified by flash chromatography[35] on 58 g of silica with 75:25 hexane–ethyl acetate to give 5.53 g (76%) of a clear viscous yellow oil. An analytical sample was obtained by preparative silica gel TLC using the same solvent system. ^{1}H NMR (250 MHz): δ 1.4–2.5 (m, 15), 2.55 (m, 1), 3.17 (tq, 1, *J* = 13.1, 1.8), 3.45–3.60 (m, 2), 3.90–4.10 (m, 4), 4.50 (s, 2), 4.97 (ddd, 1, *J* = 13.1, 5.0, 1.9), 7.35 (br s, 5). ^{13}C NMR (50 MHz): δ 24.6, 26.6, 32.0, 33.4, 36.5, 40.2, 45.8, 50.2, 60.8, 63.7, 64.3, 69.8, 72.5 , 77.7, 106.4, 127.0, 127.05, 127.15, 127.8, 138.0, 202.0. Anal. Calcd for $C_{23}H_{31}NO_3S$: C, 68.79; H, 7.78; N, 3.49. Found: C, 68.66; H, 7.83; N, 3.33.

(1″*R* + *S*,7*R,7a*R**,10a*S**)-(±)-Hexahydro-7-(1″-methyl-3″-oxobutyl)-7-[3-(phenylmethoxy)propyl]spiro[cyclopent[*i*]indolizine-2(1*H*),2′-[1,3]dioxolane]-6(7*H*)-thione (24).** To a solution of 0.577 mL (4.11 mmol) of diisopropylamine in 1.5 mL of THF at 0 °C was added 2.42 mL (4.11 mmol) of *n*-butyllithium in hexane. The resulting solution was stirred for 30 min and 1.50 g (3.74 mmol) of thiolactam **20** in 1.7 mL of THF was added dropwise. The solution was allowed to stir for 30 min and 0.402 mL (4.11 mmol) of 3-penten-2-one (**23**) was added all at once. After 10 min, the reaction mixture was poured into 30 mL of saturated NH_4Cl and then treated with 10 mL of ethyl acetate. The phases were separated, the aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and evaporated to give 2.0 g of a brownish oil. This oil was purified by flash chromatography on 97 g of silica gel with 2:1 hexane/ethyl acetate, and the resulting oil was placed in a Kugelrohr apparatus at 90–100 °C and 0.025 Torr for 3 h. A small amount of clear oil distilled. The pot residue was filtered through 20 g of silica gel with 2:1 hexane/ethyl acetate to give 1.41 g (78%) of a yellow oil. IR (film): 2960, 2875, 1710, 1478, 1435, 1195, 1105, 745 cm^{-1}. ^{1}H NMR (250 MHz): δ 0.78 and 0.86 (both d, 3, *J* = 6.5 and 6.7, 1:5 ratio, respectively), 1.4–2.0 (m, 14), 2.1–2.3 (m, 1), 2.17 (s, 3), 2.36 (d, 1, *J* = 12.8), 2.5–2.8 (m, 2), 3.07 (td, 1, *J* = 13.1, 3.0), 3.44 (m, 2), 3.98 (m, 4), 4.47 (s, 2), 5.04 (br d, 1, *J* = 13.1), 7.32 (m, 5). ^{13}C NMR (50 MHz): δ 13.8, 26.1, 26.2, 26.8, 29.4, 33.5, 34.0, 35.6, 38.7, 40.8, 45.3, 48.2, 50.3,

(34) (a) Luft, R. *Ann. Chim. (Paris)* **1959**, *4*, 745. (b) Birch, A. J.; Macdonald, P. L.; Powell, V. H. *J. Chem. Soc. C* **1970**, 1469.

(35) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

62.8, 63.9, 64.8, 70.7, 72.7, 77.2, 107.1, 127.4, 127.5, 128.3, 138.5, 204.2, 208.6. Mass spectrum (CI): *m/z* 486 (0.61), 378 (0.02), 369 (0.08), 257 (0.34). Anal. Calcd for $C_{28}H_{39}NO_4S$: C, 69.24; H, 8.09; N, 2.88. Found: C, 69.29; H, 8.07; N, 2.91.

(3a*S,12aα,12aα,12bβ)-(±)-2,3,6,7,11,12,12a,12b-Octahydro-12-methyl-12a-[3-(phenylmethoxy)propyl]spiro[cyclopenta[*b*]pyrido[1,2-*a*]indole-5(4*H*),2′-[1,3]dioxolan]-10-(1*H*)-one (25).** To a solution of 4.53 g (9.33 mmol) of **24** in 26 mL of dry, ethanol-free $CHCl_3$, under N_2 was added, in portions and under a generous flow of N_2, solid triethyloxonoium fluoborate (2.22 g, 11.7 mmol). After stirring at room temperature for 170 min, 0.1 mL of 2,6-di-*tert*-butylpyridine was added. After another 110 min, thin layer chromatography (silica, 2:1 hexane/ethyl acetate eluant) indicated that salt formation was essentially complete, and the solution was treated with 23 mL of dry $CHCl_3$ and 4.00 mL (28 mmol) of triethylamine and heated to reflux. After 46 h, the solution was cooled and treated with 50 mL of water, the phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic phase was dried (Na_2SO_4), filtered, and concentrated under vacuum to give 5 g of a red oil. Purification by flash chromatography on 111 g of silica with $CHCl_3$ and then 3% CH_3OH in $CHCl_3$ gave a yellow oil which was dried under high vacuum with heating for several hours to give 3.37 g (80%) of a yellow rigid oil. IR ($CHCl_3$): 2960, 1565, 1105. ^1H NMR (250 MHz): δ 1.05 (d, 3, J = 6.9), 1.5–2.0 (m, 12), 2.11 (d, 1, J = 17.8), 2.26 (m, 3), 2.40 (apparent t, 1, J = 6.5, 8.2), 2.71 (dd, 1, J = 17.8, 5.2), 3.14 (m, 1), 3.46 (m, 3), 3.95 (m, 4), 4.48 (s, 2), 4.92 (s, 1), 7.31 (m, 5). ^{13}C NMR (50 MHz): δ 17.2, 26.7, 27.3, 27.8, 32.7, 32.8, 34.7, 35.7, 38.6, 41.6, 46.3, 51.1, 51.8, 63.8, 64.6, 70.0, 72.9, 77.8, 91.4, 107.2, 127.3, 127.4, 128.3, 138.3, 175.1, 194.3. Mass spectrum: *m/z* 451 (0.37), 422 (0.24), 4.09 (0.64), 360 (2.73), 303 (1.53), 149 (1.79), 99 (4.03). Anal. Calcd for $C_{28}H_{37}NO_4$: C, 74.47; H, 8.26; N, 3.10. Found: C, 74.13; H, 8.32; N, 3.09.

(3a*S,8aα,12aα,12aα,12bβ)-(±)-Decahydro-12-methyl-12a-[3-(phenylmethoxy)propyl]spiro[cyclopenta[*b*]pyrido[1,2-*a*]indole-5(4*H*),2′-[1,3]dioxolan]-10(1*H*)-one (27).** To a solution of **25** (1.00 g, 2.21 mmol) in 10 mL of dry CH_2Cl_2 at 0 °C under N_2 was added trimethyloxonium fluoroborate (0.48 g, 3.25 mmol) in portions over 4.75 h, alternating with the addition of 2,6-di-*tert*-butylpyridine (0.1 mL). The solvent was removed with a rotary evaporator at or below room temperature, the residue was dissolved in 15 mL of methanol, and the solution was cooled to −25 °C. Sodium borohydride (0.43 g, large excess) was added in portions until thin layer chromatography (1:19 $CH_3OH/CHCl_3$) indicated that the salt was completely consumed. The solution was concentrated carefully at or below room temperature with a rotary evaporator, and the residue was taken up in a mixture of 10 mL of ether, 2 mL of acetic acid, and 5 mL of 10% HCl. This solution was stirred at 0–5 °C with a cooling plate for 7 days and then was treated carefully with solid K_2CO_3 and water. The solution was extracted with ethyl acetate (5 × 20 mL) and then dried (Na_2SO_4), filtered, and evaporated to give 1.0 g of a yellow oil. Purification by flash chromatography on 50 g of silica gel with 66:33 hexane/ethyl acetate followed by removal of the last traces of solvent with a Kugelrohr still at 75 °C and 0.025 Torr for 18 h gave 0.87 (87%) of a clear oil. IR ($CHCl_3$): 2955, 2875, 1710, 1360, 1070 cm^{-1}. ^1H NMR (250 MHz): δ 0.80 (d, 3, J = 6.2), 1.45 (d, 1, J = 12.7), 1.6–1.9 (m, 13), 1.96 (d, 1, J = 14.8), 2.1–2.3 (m, 4), 2.46 (s, 2), 2.70 (m, 1), 2.95 (s, 1), 3.49 (t, 2, J = 6.3), 3.8–4.0 (m, 4), 4.52 (s, 2), 7.3 (m, 5). ^{13}C NMR (50 MHz): δ 14.4, 22.6, 22.8, 23.3, 24.3, 30.4, 31.2, 35.1, 40.5, 41.0, 41.5, 43.0, 45.3, 53.0, 62.5, 63.1, 64.2, 70.7, 72.6, 72.7, 105.8, 127.3, 128.2, 138.3, 212.2. Mass spectrum: *m/z* 453 (1.1), 411 (1.0), 382 (2.2), 320 (3.7), 99 (2.81), 91 (4.1). Anal. Calcd for $C_{28}H_{39}NO_4$: C, 74.14; H, 8.67; N, 3.09. Found: C, 74.01; H, 8.53; N, 3.08.

(3a*S,8aα,12aα,12bβ)-(±)-2,3,6,7,8a,9,12a,12b-Octahydro-12-methyl-12a-[3-(phenylmethoxy)propyl]spiro[cyclopenta[*b*]pyrido[1,2-*a*]indole-5(4*H*),2′-[1,3]dioxolan]-10-(1*H*)-one (29).** To a solution of 0.253 mL (1.51 mmol) of 2,2,6,6-tetramethylpiperidine in 1.0 mL of THF at 0 °C was added 1.00 mL (1.51 mmol) of *n*-butyllithium in hexane. The solution was stirred at 0 °C for 30 min, cooled to −78 °C, and treated with a solution of 0.488 g (1.08 mmol) of **27** in 2.2 mL of THF. The solution was stirred at −78 °C for 165 min and then treated with 0.309 g (1.61 mmol) of benzeneselenenyl chloride in 1.2 mL of THF. The mixture was stirred for an additional 45 min and then poured into 15 mL of 1% aqueous NaOH. The layers were separated, the aqueous layer was extracted with ethyl acetate (5 × 15 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and evaporated to give 0.801 g of a yellow oil. This material was partially purified by flash chromatography on 45 g of silica with 3:1 hexane/EtOAc to remove nonpolar selenium-containing byproducts. This procedure gave 0.64 g of a yellow oil that was dissolved in 5 mL of CH_2Cl_2 and 1 mL of CH_3OH, cooled to −78 °C, and treated with 0.215 g (1.00 mmol) of 80% chloroperoxybenzoic acid in 1.5 mL of methanol. The solution was allowed to warm to −20 °C over 1 h and was stirred at −10 to −30 °C for an additional hour. The reaction mixture was poured into 15 mL of 1% NaOH, the layers were separated, and the aqueous layer was extracted with ethyl acetate (5 × 16 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to give 0.700 g of a yellow oil. Purification by flash chromatography on 41 g of silica gel with 2:1 hexane/ethyl acetate gave 0.285 g (59%) of a light yellow oil that crystallized on standing, mp 119–125 °C. On recrystallization from ether, colorless crystals, mp 125.5 °C, were obtained. IR ($CHCl_3$): 2940, 2860, 1670 cm^{-1}. ^1H NMR (250 MHz): δ 1.2–2.0 (m, 17), 2.1 (m, 1), 2.32 (td, 1, J = 11.0, 4.2), 2.56 (m, 2), 2.85 (m, 1), 3.04 (br s, 1), 3.45 (m, 2), 3.90 (m, 4), 4.49 (s, 2), 5.78 (s, 1), 7.3 (m, 5). ^{13}C NMR (50 MHz): δ 20.4, 24.8, 25.0, 25.3, 26.0, 30.9, 35.2, 38.6, 39.7, 44.3, 50.4, 58.3, 62.9, 63.3, 64.3, 70.4, 72.4, 72.9, 108.8, 125.6, 127.5, 127.6, 128.3, 138.3, 163.6, 198.0. Mass spectrum: *m/z* 451 (0.12), 408 (0.13), 302 (1.62), 135 (4.15), 57 (7.04). Anal. Calcd for $C_{28}H_{37}NO_4$: C, 74.47; H, 8.26; N, 3.10. Found: C, 74.22; H, 8.32; N, 3.03.

(3aα,4α,7aβ,10aβ,10bα,10cα)-(±)-3a,4,5,6,8,9,10,10a,10b,10c-Decahydro-4-hydroxy-1-methyl-10b-[3-(phenylmethoxy)propyl]-4,7a-methano-3*H*,7a*H*-cyclopenta[4,5]pyrrolo[3,2,1-*ij*]quinolin-3-one (30). Enone **29** (0.019 g, 0.042 mmol) was dissolved in a mixture of 1 mL of acetone, 0.5 mL of 10% HCl, and 10 drops of H_2SO_4. The solution was stirred at room temperature for 8 h, and the solution was concentrated, cooled to 0 °C, treated with ether, and carefully made basic with K_2CO_3. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 4 mL), dried (Na_2SO_4), filtered, and evaporated to give 19.6 mg of an oil. This material was usually carried on to **31** as is, but could be purified by flash chromatography on silica gel with 3% CH_3OH in $CHCl_3$. IR ($CHCl_3$): 3430, 3010, 2960, 2870, 1685 cm^{-1}. ^1H NMR (250 MHz): δ 1.2–1.95 (m, 15), 1.99 (s, 3), 2.41 (d, 1, J = 9.8), 3.1 (m, 2), 3.5 (m, 2), 3.68 (d, 1, J = 9.8), 4.50 (s, 2), 4.52 (s, 1), 5.94 (s, 1), 7.3 (m, 5). ^{13}C NMR (50 MHz): δ 21.7, 26.4, 26.8, 27.3, 29.9, 36.8, 37.2, 39.7, 45.9, 47.7, 49.9, 65.9, 66.4, 70.1, 70.2, 72.9, 73.4, 126.6, 127.5, 128.3, 138.4, 170.5, 200.8. Mass spectrum: *m/z* 407 (0.08), 390 (0.5), 316 (2.0), 301 (2.6), 286 (1.9), 258 (5.7), 1.52 (4.0), 91 (5.3). Anal. Calcd for $C_{26}H_{33}NO_3$: C, 76.62; H, 8.16; N, 3.44. Found: C, 76.50; H, 8.13; N, 3.38.

(3aα,6α,6aβ,10α,10aβ,10bα)-(±)-Octahydro-6a-methyl-10a-[3-(phenylmethoxy)propyl]-1*H*-3a,10,6-(nitrilomethano)benz[*e*]azulene-5,8(4*H*,6*H*)-dione (31). A solution of **30** (0.017 g, 0.042 mmol) in 2 mL of methanol was added to a solution of 1 mL of methanol containing sodium methoxide (from a small piece of sodium (≤1 mg), and the yellow solution was stirred until TLC (5% CH_3OH in $CHCl_3$) indicated that **30** was essentially gone (8 h). At this point, the reaction mixture was cooled to 0 °C and treated with a few drops of saturated NH_4Cl. The solution was carefully evaporated and then treated with saturated K_2CO_3. The mixture was extracted with $CHCl_3$ (4 × 4 mL), dried (Na_2SO_4·K_2CO_3), filtered, and evaporated to give 0.021 g of an oily solid. Purification by flash chromatography on 1.5 g of silica with 1:98 methanol/$CHCl_3$ gave 0.012 g (70%) of **3** as an oily solid. IR ($CHCl_3$): 2960, 2920, 1715, 1455, 1100 cm^{-1}. ^1H NMR (250 MHz): δ 1.04 (s, 3), 1.2–2.0 (m, 12), 2.21 (d, 1, J = 18.9), 2.28 (d, 1, J = 16.6), 2.55 (dd, 1, J = 18.9, 5.9), 2.59 (d, 1, J = 18.4), 2.81 (d, 1, J = 18.9), 2.85 (d, 1, J = 16.6), 2.97 (dd, 1, J = 16.1, 2.4), 3.08 (d, 1, J = 16.1), 3.31 (d, 1, J = 5.9), 3.38 (m, 2), 4.48 (s, 2), 7.3 (m, 5). ^{13}C NMR (50 MHz): δ 23.9, 25.5, 27.7., 27.9, 29.9, 39.1, 39.8, 42.5, 44.3, 46.2, 48.6, 52.5, 56.9, 57.8, 64.0, 69.9, 70.8, 73.0, 127.5, 127.7, 128.4, 138.2, 209.5, 211.3. Mass spectrum: *m/z* 407 (3.7), 316 (3.1), 258 (2.8), 216 (1.6), 91 (9.0). Anal. Calcd for $C_{26}H_{33}NO_3$: C, 76.62; H, 8.16; N, 3.44. Found: C, 76.39; H, 8.23; N, 3.39.

(3aα,6α,6aβ,9E,10α,10β,10bβ)-(±)-9-Ethylideneoctahydro-6a-methyl-10a-[3-(phenylmethoxy)propyl]-1H-3a,10,6-(nitrilomethano)benz[e]azulene-5,8(4H,6H)-dione (36). In a dry 2-necked 25-mL flask attached to an N_2/vacuum manifold through one neck and equipped with a septum on the other was placed 0.48 mL (3.40 mmol) of diisopropylamine in 1.8 mL of THF under N_2. The stirring solution was cooled to 0 °C and treated with 2.01 mL (3.40 mmol) of a 1.69 M solution of *n*-butyllithium in hexane. After stirring for 0.5 h at 0 °C, the septum was exchanged for a fresh one under a generous flow of N_2, the manifold was switched to vacuum, and the solvent was carefully removed, leaving a pale yellow sludge. The vessel was again blanketed with N_2, cooled to 0 °C, and treated with 1 mL of THF to dissolve the solids. The solution was then cooled to −78 °C and to it was added enone **29** in 4 mL of THF (1.23 g, 2.72 mmol). After 110 min at −78 °C, the solution was treated with 0.39 mL (6.81 mmol) of freshly distilled acetaldehyde in 0.4 mL of THF. After 4 min, the solution was treated with 3 mL of saturated aqueous NH_4Cl and allowed to warm to room temperature. It was then treated with water and ethyl acetate, and sufficient solid Na_2CO_3 was added to render the aqueous phase basic. The layers were separated, and the aqueous layer was extracted with ethyl acetate (4 × 20 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a yellow oily solid. Absence of starting material was most easily ascertained by examination of the 5.6–6.0-ppm region of the ^1H NMR spectrum. The starting material has a singlet at 5.78 ppm, while the product aldols show singlets at 5.85 ppm (major) and 5.91, 5.77, and 5.69 ppm (minor).

The foregoing mixture was dissolved in 120 mL of acetone from a freshly opened bottle and treated with 3 mL of concd H_2SO_4. After being stirred at room temperature for 16 h, the mixture was concentrated carefully under reduced pressure below room temperature, and the black residue was treated with water and then carefully made basic with solid K_2CO_3. This solution was extracted with ethyl acetate (5 × 35 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 2.1 g of a red oil. This oil was subjected to flash chromatography on 44 g of silica with 50:50 hexane/ethyl acetate and then 6% CH_3OH in $CHCl_3$ to obtain a less polar fraction consisting mostly of **37** and a more polar fraction containing mostly the two double-bond isomers of **36**. This latter material was purified by flash chromatography on 37 g of silica with 3% CH_3OH in ethyl acetate to give 0.81 g (69%) of **36** as a yellow oil. IR ($CHCl_3$): 2960, 2870, 1720, 1685, 1620, 1450 cm^{-1}. ^1H NMR (250 MHz): δ 1.60 (s, 3), 1.1–2.1 (m, 12), 1.96 (d, 3, *J* = 7.3), 2.29 (d, 1, *J* = 19.9), 2.31 (d, 1, *J* = 16.9), 2.64 (d, 1, *J* = 19.9), 2.88 (d, 1, *J* = 17.0), 2.98 (d, 1, *J* = 15.1), 3.08 (dd, 1, *J* = 15.5, 2.4), 3.33 (t, 2, *J* = 6), 3.88 (s, 1), 4.45 (s, 2), 7.26 (q, 1, *J* = 7.2), 7.25–7.4 (m, 5). ^{13}C NMR (50 MHz): δ 14.0, 23.8, 25.5, 27.3, 27.6, 29.8, 40.2, 42.9, 46.4, 49.2, 51.2, 56.9, 58.5, 63.0, 70.2, 70.8, 72.9, 127.5, 128.3, 132.8, 138.2, 142.6, 198.0, 211.8. Mass spectrum: *m/z* 433 (8.0), 342 (5.1), 284 (2.5), 150 (1.7), 91 (5.6). Anal. Calcd for $C_{28}H_{35}NO_3$: C, 77.56; H, 8.14; N, 3.23. Found: C, 77.25; H, 8.13; N, 3.16.

(3aα,6α,7β,8E,8aβ,9α,9aα,11R*,12S*)-(±)-8-Ethylidenedecahydro-7-hydroxy-11-methyl-9-[3-(phenylmethoxy)propyl]-6,3a,9,7-[1,2,3,4]butanetetrayl-3aH-cyclopent[b]indolizin-13-one (37). The less polar fraction was purified by flash chromatography on 9 g of silica with 3% methanol/CH_3OH in $CHCl_3$ to give 0.153 g (13%) of **37** as a yellow oil. An analytical sample was obtained by formation of the HCl salt: a sample of **37** was dissolved in ether and treated with gaseous HCl. The resulting precipitate was recrystallized from ethanol; mp 245–250 °C dec, 257 °C, melting of black residue (rapid heating). IR ($CHCl_3$): 3600, 3400, 2940, 2880, 1700, 1455, 1100 cm^{-1}. ^1H NMR (250 MHz): δ 1.02 (s, 3), 1.2–2.0 (m, 10), 1.74 (d, 3, *J* = 7.0), 2.0–2.35 (m, 3), 2.16 (d, 1, *J* = 1.8), 2.38 (s, 1), 2.47 (br s, 1), 2.72 (d, 1, *J* = 13.8), 3.23 (dd, 1, *J* = 13.9, 3.0), 3.43 (t, 2, *J* = 6.4), 4.50 (s, 2), 4.63 (s, 1), 5.92 (q, 1, *J* = 7.0), 7.2–7.4 (5 H, m). ^{13}C NMR (50 MHz): δ 12.4, 21.7, 23.1, 25.6, 26.2, 26.5, 29.2, 46.2, 47.8, 52.3, 59.5, 60.8, 63.0, 70.9, 72.9, 74.2, 86.7, 118.6, 127.6, 128.3, 137.2, 138.4, 215.3. Anal. Calcd for $C_{28}H_{36}ClNO_3$: C, 71.55; H, 7.72; N, 2.98. Found: C, 71.71; H, 7.86; N, 2.96.

(±)-3,4-Didehydro-4-[(diethoxyphosphinyl)oxy]-23-(phenylmethoxy)daphnan-14-one (46). To a suspension of cuprous bromide–dimethyl sulfide complex (113.1 mg, 1.1 equiv) in dry ether (1.2 mL) under N_2 at 0 °C was added dropwise a solution of methyllithium (0.73 mL of a 1.50 M solution in ether; 2.2 equiv), and the resulting colorless solution was stirred at 0 °C for 5 min and then cooled to −78 °C over 10 min. To this stirring solution was then added a solution of **36** (216 mg, 0.50 mmol) in dry THF (1.0 mL) dropwise, and the resulting yellow mixture was warmed to 0 °C over 50 min. To this cloudy yellow mixture was then added dropwise a solution of freshly distilled diethyl phosphorochloridate (0.17 mL; 2.4 equiv) and triethylamine (0.15 mL; 2.2 equiv) in dry THF (0.2 mL). The yellow solution was warmed to room temperature with the cooling bath over 2 h and then treated with saturated aqueous NH_4Cl (3 mL), Na_2CO_3 (0.1 g), water (1 mL), and ethyl acetate (4 mL). The resulting blue solution was agitated, the layers were separated, and the aqueous phase was extracted with ethyl acetate (4 × 4 mL). The combined organic phase was then dried (Na_2SO_4) and filtered and the solvents were removed to obtain a viscous yellow oil. This material was purified by flash chromatography on silica gel (230–400 mesh; 20 g; eluted with 98:2 $CHCl_3$/methanol) to obtain 240 mg (82%) of **46** as a yellow oil. IR ($CHCl_3$): 1715, 1685, 1280, 1035, 980 cm^{-1}. ^1H NMR (250 MHz): δ 0.95 (m, 1), 1.03 (s, 3), 1.03 (d, 3, *J* = 6.9), 1.06 (d, 3, *J* = 7.0), 1.35 (br t, 6, *J* = 7.1), 1.41–2.12 (complex, 11), 2.18 (dd, 1, *J* = 18.7, 2.0), 2.23 (d, 1, *J* = 16.9), 2.51 (dd, 1, *J* = 18.7, 2.5), 2.86 (d, 1, *J* = 14.8), 2.88 (d, 1, *J* = 17.5), 3.14 (heptet, 1, *J* = 6.9), 3.33 (m, 3), 3.61 (dd, 1, *J* = 14.8, 2.6), 4.17 (quintet of d, 4, *J* = 7.0, 2.6), 4.46 (s, 2), 7.21–7.40 (m, 5). ^{13}C NMR (50 MHz): δ 16.0, 16.1, 19.7, 20.9, 23.7, 25.4, 26.3, 27.3, 27.6, 30.0, 40.2, 42.2, 42.6, 42.9, 46.2, 49.2, 55.7, 59.4, 62.9, 64.1, 64.2, 70.2, 71.1, 72.7, 123.4, 123.6, 127.4, 128.2, 138.4, 145.4, 145.5, 212.9. Anal. Calcd for $C_{33}H_{48}NO_6P$: C, 67.67; H, 8.26; N, 2.39. Found: C, 67.41; H, 8.18; N, 2.35.

(±)-3,4,13,14-Tetradehydro-23-(phenylmethoxy)daphnane-4,14-diol Bis(diethyl phosphate ester) (47). To a solution of freshly distilled diisopropylamine (0.12 mL; 2.0 equiv) in dry THF (0.75 mL) at 0 °C under N_2 was added dropwise *n*-butyllithium (0.46 mL of a 1.74 M solution in hexanes; 2.0 equiv), and the resulting solution was stirred at 0 °C for 15 min and then cooled to −78 °C over 10 min. To this stirring solution was then added a solution of **46** (240.0 mg; 0.41 mmol) and HMPA (0.28 mL; 4.0 equiv) in dry THF (1.5 mL) dropwise, and the solution was warmed to 0 °C over a 50-min period. To this mixture was then added a solution of freshly distilled diethyl phosphorochloridate (0.18 mL, 3.0 equiv) in THF (0.15 mL), and the mixture was warmed to room temperature with the cooling bath over 16 h. To the resulting solution was added saturated aqueous NH_4Cl (2 mL), water (1 mL), Na_2CO_3 (0.1 g), and ethyl acetate (4 mL), and the mixture was agitated and the layers were separated. The aqueous phase was extracted with ethyl acetate (4 × 4 mL) and the combined organic phase was dried ($MgSO_4$). Filtration and removal of solvent gave a mobile yellow oil that was subjected to Kugelrohr distillation (75 °C at 0.05 mmHg) and gave a yellow oil after 2 h. This material was purified by column chromatography on silica gel (70–230 mesh, 7 g, eluted with 98:2 $CHCl_3$/methanol) to obtain 216.2 mg (73%) of pure **47** as a yellow oil. IR ($CHCl_3$): 3500, 3400, 1680, 1260, 1030 cm^{-1}. ^1H NMR (250 MHz): δ 0.87 (m, 1), 1.03 (t, 6, *J* = 6.5), 1.08 (s, 3), 1.35 (m, 12), 1.41–1.93 (complex, 9), 2.10 (m, 1), 2.12 (br d, 1, *J* = 18.9), 2.35–2.60 (complex, 3), 3.12 (septet, 1, *J* = 6.9), 3.32 (t, 3, *J* = 6.7), 3.71 (dd, 1, *J* = 12.6, 2.9), 4.15 (m, 8), 4.46 (s, 2), 5.74 (s, 1), 7.21–7.41 (complex, 5). ^{13}C NMR (50 MHz): δ 16.0, 16.1, 19.5, 21.0, 24.2, 26.4, 26.8, 27.7, 28.0, 28.9, 37.1, 40.8, 42.3, 51.5, 52.0, 52.8, 52.9, 58.3, 63.0, 64.0, 64.1, 64.3, 64.4, 71.2, 72.7, 73.2, 119.2, 119.3, 124.0, 124.9, 127.4, 128.2, 138.4, 145.7, 145.8, 156.4, 156.6. Anal. Calcd for $C_{37}H_{57}NO_9P_2$: C, 62.57; H, 7.96; N, 1.94. Found: C, 61.83; H, 8.04; N, 2.17.

(±)-3,4-Didehydrodaphnan-23-ol (48). Ethylamine (7 mL) was distilled from lithium into a 3-necked flask equipped with a dry ice/2-propanol-cooled cold finger, an outlet to an argon supply, and a septum. The vessel was cooled to −78 °C and, under a gaseous stream of argon, lithium metal (0.055 g, 7.8 mmol) was added. Within 5 min, the stirring solution became blue and the flask was warmed to 0 °C. To this solution was added a mixture of **47** (93.8 mg, 0.13 mmol) and dry *tert*-butyl alcohol (0.29 mL) in dry THF (0.6 mL) dropwise over 6 min. After 20 min more, water (0.5 mL) was added and most of the ethylamine was blown

off with a stream of air. The resulting white solid was dissolved in water (2 mL) and ethyl acetate (3 mL), the layers were separated, and the aqueous phase was extracted with ethyl acetate (5 × 6 mL). The combined organic phase was dried (Na_2SO_4–K_2CO_3), filtered, and concentrated to give 200 mg of a mobile yellow oil. The product was purified by flash chromatography on silica gel (230–400 mesh) with 95:5 $CHCl_3$/methanol, then 98:1.5:0.5 CH_2Cl_2/methanol/concd NH_4OH, and finally 95:4.5:0.5 CH_2Cl_2/methanol/concd NH_4OH to obtain 27.2 mg (64%) of pure **48** as a colorless oil. An analytical sample, mp 119–120 °C, was prepared by sublimation in a Kugelrohr apparatus (110 °C at 0.03 Torr) for 2 h. IR ($CHCl_3$): 3620, 2960, 2870, 1460, 1380 cm^{-1}. ^1H NMR (250 MHz): δ 0.86 (m, 1), 0.98 (s, 3), 1.02 (d, 3, J = 7.0), 1.05 (d, 3, J = 7.0), 1.21–2.01 (m, 16), 2.05–2.25 (complex m, 3), 2.57 (d, 1, J = 13.6), 3.05 (s, 1), 3.20 (d, 1, J = 13.6), 3.48 (t, 2, J = 6.8), 5.80 (t, 1, J = 3.0). ^{13}C NMR (50 MHz): δ 21.3, 22.0, 22.4, 24.6, 25.5, 27.0, 28.2, 29.4, 30.8, 33.6, 37.9, 41.6, 42.4, 43.0, 44.1, 48.1, 50.9, 64.0, 65.0, 73.0, 126.5, 139.7. Mass spectrum: m/z 329 (10.1), 314 (4.5), 300 (2.1), 270 (8.6), 219 (2.4), 140 (2.6), 109 (1.7). Anal. Calcd for $C_{22}H_{35}NO$: C, 80.19; H, 10.71; N, 4.25. Found: C, 80.19; H, 10.81; N, 4.44.

(±)-3,4-Didehydrohomodaphniphyllic Acid (49). To a solution of **48** (7.0 mg, 0.021 mmol) in acetone (1.2 mL) at 0 °C was added Jones reagent (0.05 mL) dropwise with stirring. The resulting orange solution was stirred under these conditions for 35 min. The cooling bath was then removed and 2-propanol (0.1 mL) was added dropwise, whereupon a green precipitate formed immediately. This mixture was stirred at room temperature for 20 min and filtered through a short plug of Celite. The flask and the Celite pad were washed with acetone (1.0 mL), and the solvent was removed and yellow oil was obtained that was purified by flash chromatography on silica gel (230–400 mesh, 0.7 g, eluted with 79:19:2 $CHCl_3$/methanol/concd NH_4OH to obtain 6.0 mg (82%) of **49** as an amorphous white solid. ^1H NMR (250 MHz): δ 0.91 (m, 1), 0.99–1.06 (complex m, 9), 1.25–2.46 (complex m, 19), 3.19 (br d, 1, J = 12.8), 3.36 (br d, 1, J = 10.8), 3.63 (s, 1), 6.02 (br s, 1). HRMS: calcd for $C_{22}H_{33}NO_2$ 343.2513, found 343.2502.

(±)-Methyl 3,4-Didehydrohomodaphniphyllate (50). To **49** (3.0 mg, 0.009 mmol) at room temperature was added methanolic HCl (3.0 mL of a 20% w/w solution), and the resulting mixture was heated at reflux for 24 h and then cooled to room temperature. The solvent was removed under reduced pressure and the resulting white solid was purified by flash chromatography on silica gel (230–240 mesh, 0.5 g, eluted with 95:3:2 $CHCl_3$/methanol/concd NH_4OH) to obtain 2.8 mg (89%) of pure **50** as a colorless oil. IR ($CHCl_3$): 2980, 1745, 1435, 1250 cm^{-1}. ^1H NMR (250 MHz): δ 0.95 (s, 3), 1.03 (d, 3, J = 6.7), 1.05 (d, 3, J = 6.7), 1.19–1.94 (complex, 14), 2.09–2.31 (complex, 3), 2.45 (m, 2), 2.60 (d, 1, J = 13.9), 3.08 (s, 1), 3.21 (br d, 1, J = 13.6), 3.65 (s, 3), 5.82 (br t, 1, J = 2.8). ^{13}C NMR (125 MHz): δ 21.07, 21.50, 22.18, 23.88, 25.30, 25.48, 27.78, 29.39, 31.66, 32.74, 37.75, 40.11, 41.66, 42.10, 43.21, 47.27, 50.52, 51.75, 64.44, 77.41, 173.88. Mass spectrum: m/z 357 (base), 344 (47.4), 328 (14.0), 316 (9.2), 286 (14.7), 270 (47.7), 137 (58.4). HRMS: calcd for $C_{23}H_{35}NO_2$ 357.2670, found 357.2667.

(±)-Methyl 3-Epihomodaphniphyllate (51). Into a cylindrical glass tube (22-mm outside diameter) with a flat bottom and a 24-mm outside diameter lip were placed a solution of **50** (5.2 mg, 0.0146 mmol) in toluene (2.5 mL) and 6 mg of 5% Rh on Al_2O_3 (Engelhart Lot 8334) and a pea stir bar. The tube was placed in a small pressure vessel (1.0-in. inside diameter Parr screw cap bomb, Model No. 4714 with gauge block assembly), which was closed, sealed, and pressurized to 1800 psi with H_2 directly from a hydrogen tank and then vented to room pressure. This process was repeated three times after which the bomb was pressurized to 1800 psi with H_2 and the bomb placed in an oil bath mounted on a magnetic stirrer. The bomb was heated at 120 °C with stirring for 2 h at which point the pressure had dropped to 800 psi. It was refilled to 1800 psi and heated at 120 °C with stirring for 18 h total. The bomb was then removed from the oil bath and cooled to room temperature over 2 h before the H_2 pressure was released and the bomb opened. The glass tube was removed and the black heterogeneous reaction mixture was passed through a short plug of Celite (eluted with $CHCl_3$, then methanol). The solvents were removed under reduced pressure and the resulting white film was purified by flash chromatography on silica gel (230–400 mesh, 0.8 g, eluted with 95:3:2 $CHCl_3$/methanol/concd NH_4OH) to obtain 4.6 mg (88%) of **51** as a colorless oil. Silica gel TLC (eluted with 95:3:2 $CHCl_3$/methanol/concd NH_4OH) gave one spot (R_f = 0.22) when developed in an iodine chamber. IR ($CHCl_3$): 2970, 1740, 1455, 1180 cm^{-1}. ^1H NMR (500 MHz, C_6D_6): δ 0.89 (s, 3), 0.94 (d, 3, J = 6.3), 1.15 (d, 3, J = 6.2), 1.16–1.88 (complex m, 19), 2.15 (m, 1), 2.49 (m, 2), 2.72 (d, 1, J = 14.2), 2.90 (s, 1), 3.22 (dt, 1, J = 14.2, 2.8), 3.50 (s, 3). Mass spectrum: m/z 359 (22.2), 344 (base), 316 (17.4), 286 (29.7), 272 (29.6), 137 (72.9). HRMS: calcd for $C_{23}H_{37}NO_2$ 359.2826, found 359.2822.

The hydrochloride salt of **51** was prepared by addition of an ethereal HCl solution (prepared by bubbling HCl through ether at 0 °C for 10 min) to **51**, followed by removal of solvent after 10 min at room temperture. ^1H NMR (500 MHz): δ 0.99 (d, 3, J = 6.5), 1.07 (s, 3), 1.18 (d, 3, J = 6.6), 1.41–1.70 (complex, 8), 1.76 (m, 1), 1.86–2.09 (complex m, 5), 2.10–2.16 (complex m, 3), 2.23 (m, 1), 2.41 (m, 2), 2.51 (m, 1), 3.20 (d, 1, J = 13.7), 3.60 (s, 1), 3.61 (m, 1), 3.69 (s, 3).

(3β)-(±)-Daphnan-23-ol (52). The hydrogenation apparatus and procedure described for the preparation of **51** was employed to reduce 4.1 mg (0.012 mmol) of amino alcohol **48** in 1.5 mL of absolute ethanol; 4.1 mg of 5% Rh on Al_2O_3 was used. After 20 h at 120 °C and 1800 psi H_2, the bomb was cooled, and opened, and the heterogeneous reaction mixture was processed as before to obtain a clear oil. This material was subjected to flash chromatography on silica gel, eluting with 89:9:2 $CHCl_3$/methanol/concd NH_4OH, to obtain 3.5 mg (85%) as a colorless oil. IR ($CHCl_3$): 2960, 1460, 1370, 1250 cm^{-1}. Mass spectrum: m/z 333 (36.1), 316 (base), 286 (18.3), 272 (32.2), 238 (29.0), 137 (29.3). ^1H NMR (250 MHz): δ 0.83–2.24 (complex m, 22), 0.98 (d, 3, J = 6.5), 1.11 (s, 3), 1.17 (d, 3, J = 6.5), 2.41 (m, 1), 3.20 (d, 1, J = 13.1), 3.51–3.69 (complex m, 4). HRMS: calcd for $C_{22}H_{37}NO$ 331.2875; found 331.2885.

(±)-Daphnan-23-ol (53). A mixture of amino alcohols **52** and **53** (1:1) was produced by the same hydrogenation technique reported above, using $Pd(OH)_2$ on carbon (1:1 w/w Aldrich Lot 1227 LL). This procedure gave an 87% yield of **52** and **53** (1:1) as a colorless oil after flash chromatography on silica gel (230–400 mesh, 0.8 g, eluted with 89:9:2 $CHCl_3$/methanol/concd NH_4OH. Properties for **53**: IR ($CHCl_3$): 2960, 1465, 1395, 1370, 1250 cm^{-1}. ^1H NMR (250 MHz): δ 0.82–2.36 (complex m, 23), 0.95 (d, 3, J = 6.6), 1.06 (s, 3), 1.14 (d, 3, J = 6.3), 3.39 (m, 1), 3.47–3.78 (complex m, 4). HRMS: calcd for $C_{22}H_{37}NO$ 331.2875; found 331.2876.

(±)-Methyl Homodaphniphyllate (2). The hydrogenation apparatus described for the preparation of **51** was used to reduce 6.0 mg (0.0175 mmol) of amino acid **49** in 2.0 mL of methanol; 6.0 mg of $Pd(OH)_2$ on carbon (Aldrich Lot 1227 LL) was used. After 24 h at 120 °C and 1800 psi H_2 the bomb was cooled and opened and the heterogeneous reaction mixture processed as before to obtain a crude product that was purified by flash chromatography on silica gel, eluting with 95:3:2 $CHCl_3$/methanol/concd NH_4OH, to obtain 5.1 mg (81%) of a 1:1 mixture of **2** and **51**. Compounds **2** and **51** separate easily on silica gel TLC plates (eluant 95:3:2 $CHCl_3$/methanol/concd NH_4OH), giving R_f 0.33 and 0.22, respectively. The isomers were separated by careful flash chromatography on 230–400-mesh silica gel, eluting with the same solvent system. Pure (±)-**2** was obtained as a colorless oil. IR ($CHCl_3$): 2960, 1735, 1380, 1250, 1060 cm^{-1}. Mass spectrum: m/z 359 (70.6), 344 (62.8), 286 (31.6), 272 (54.7), 57 (base). ^1H NMR (500 MHz, C_6D_6): δ 0.77 (s, 3), 0.98 (d, 3, J = 6.6), 1.09 (dd, 1, J = 8.6, 3.4), 1.24 (d, 3, J = 6.5), 1.25–1.87 (complex m, 18), 2.16 (m, 1), 2.47 (m, 2), 2.75 (d, 1, J = 14.8), 2.79 (d, 1, J = 5.2), 3.19 (dt, 1, J = 14.2, 3.0), 3.52 (s, 3). HRMS: calcd for $C_{23}H_{37}NO_2$ 359.2826, found 359.2835.

The foregoing synthetic material was identified by comparison with a sample of the natural alkaloid. The material supplied to us by Professor S. Yamamura was the hydrochloride salt of methyl homodaphniphyllate. It had mp 231–33 °C (sealed capillary). ^1H NMR (500 MHz, $CHCl_3$): δ 0.95 (d, 3, J = 6.5), 1.03 (s, 3), 1.15 (d, 3, J = 6.2), 1.38–2.08 (complex m, 16), 2.17 (m, 2), 2.31 (m, 1), 2.39 (m, 2), 2.53 (m, 1), 3.38 (m, 2), 3.57 (br d, 1, J = 14.0), 3.69 (s, 3).

The free base was prepared by dissolving the hydrochloride in 95:3:2 $CHCl_3$/methanol/concd NH_4OH and chromatographing

this solution on 0.5 g of 230-400-mesh silica gel, eluting with the same solvent. The free base had R_f 0.33 when analyzed by TLC on silica gel with the same solvent system.

Because the amounts of (±)-2 and natural 2 at our disposal were very small (on the order of 1 mg each), we were unable to make a valid ^{1}H NMR comparison in $CDCl_3$ solution. It appears that only trace amounts of adventitious acid can give rise to extensive broadening of certain peaks. However, the ^{1}H NMR spectra of C_6D_6 were quite reproducible. ^{1}H NMR spectra of the synthetic and natural alkaloids are shown in the supplementary material.

Acknowledgment. This work was supported by a research grant from the National Science Foundation (CHE-84-18437). We are indebted to Professors Y. Hirata and S. Yamamura for authentic samples of codaphniphylline and methyl homodaphniphyllate.

Registry No. (±)-2, 104115-43-7; (±)-4, 104115-44-8; (±)-5, 138489-23-3; (±)-6, 138489-24-4; 8, 62240-37-3; 8 (phthalimide derivative), 84764-41-0; (±)-9, 138489-25-5; (±)-10, 104115-45-9; (±)-11, 104115-46-0; 13, 23769-10-0; (±)-15, 138489-26-6; (±)-16, 104115-47-1; (±)-17 (isomer 1), 138489-27-7; (±)-17 (isomer 2), 138602-80-9; 19, 138489-28-8; (±)-20, 104115-48-2; (±)-21 (isomer 1), 138604-10-1; (±)-21 (isomer 2), 138489-29-9; 22 (2″-ene isomer), 138489-31-3; 22 (3″-ene isomer), 138489-30-2; 23, 3102-33-8; (±)-24 (isomer 1), 138602-81-0; (±)-24 (isomer 2), 138602-82-1; (±)-25, 138602-83-2; (±)-27, 138602-84-3; (±)-28, 138489-32-4; (±)-29, 104115-52-8; (±)-30, 138489-33-5; (±)-31, 138489-34-6; (±)-32, 138489-35-7; (±)-33, 138489-36-8; (±)-34a, 138489-37-9; (±)-34b, 138489-38-0; (±)-36, 104115-53-9; (±)-37·HCl, 138516-33-3; (±)-43, 138515-96-5; (±)-44, 138602-86-5; (±)-46, 104115-54-0; (±)-47, 138489-39-1; (±)-48, 104115-56-2; (±)-49, 138515-97-6; (±)-50, 104115-57-3; (±)-51, 104154-52-1; (±)-51·HCl, 138515-98-7; (±)-52, 104115-58-4; (±)-53, 104154-53-2; $BnO(CH_2)_3Br$, 54314-84-0; methyl (±)-2-oxocyclopentanecarboxylate, 53229-93-9; ethyl (±)-1-(methoxycarbonyl)-2-oxocyclopentanecarboxylate, 122040-88-4.

Supplementary Material Available: A poem by Suimei Kawai, *Yuzuri-ha*, in the original Japanese and an English translation, a more detailed discussion of the network analysis of methyl homodaphniphyllate, experimental procedures for compounds 4, 5, 6, 9, 17, 21, 22, 32, 33, 34, 35, 43, and 44, and ^{1}H NMR spectra of compounds 34a, 34b, 35, 43, 44, 49, 50, 51, 52, and 53 (21 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and may be ordered from the ACS; see any current masthead page for ordering information.

Daphniphyllum Alkaloids. 11. Biomimetic Total Synthesis of Methyl Homosecodaphniphyllate. Development of the Tetracyclization Reaction[1]

Clayton H. Heathcock,* Marvin M. Hansen,[2a] Roger B. Ruggeri,[2b] and John C. Kath

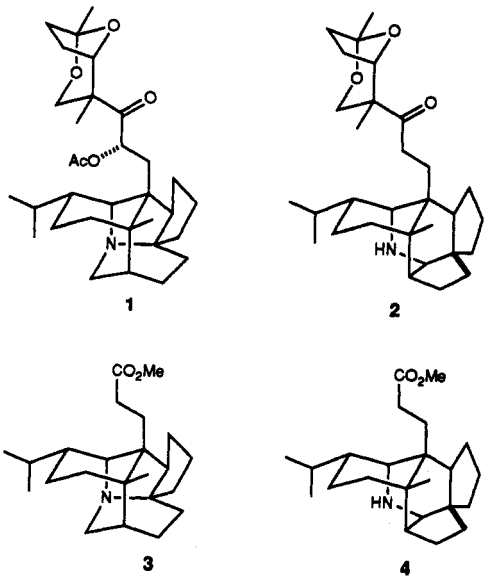
Department of Chemistry, University of California, Berkeley, California 94720

Received August 6, 1991

A biomimetic total synthesis of (±)-methyl homosecodaphniphyllate has been developed. The synthesis starts with a triply convergent, tandem Michael addition–enolate alkylation, wherein amide 9, enoate 7, and alkyl iodide 5 are assembled in essentially quantitative yield to obtain compounds 13, 14, and 15. The major isomer 13 is converted in three steps into a 1:1 mixture of diols 18a and 18b. These diols are subjected to a two-step process involving Swern oxidation and treatment of the resulting dialdehyde sequentially with ammonia and acetic acid; pentacyclic unsaturated amine 23 is obtained in 82% yield. Three additional functional group steps are used to convert 23 into racemic methyl homosecodaphniphyllate ((±)-4). The synthesis requires nine steps and proceeds in 48% overall yield from 5, 7, and 9. The tetracyclization process was shown to proceed via dialdehyde 26, tricyclic aza diene 27, and tetracyclic imine 28. An interesting and potentially useful variant of the tetracyclization procedure employs methylamine or benzylamine instead of ammonia. In this modification, the final reaction product is pentacyclic amine 29, in which the isopropenyl double bond has also been reduced. It is suggested that this reduction occurs by intramolecular hydride transfer at the stage of cationic intermediate 33.

Daphniphylline (1) and secodaphyniphylline (2) represent two of the three basic classes of C-30 *Daphniphyllum* alkaloids. They are accompanied in nature by their C-22 counterparts, methyl homodaphniphyllate (3) and methyl homosecodaphniphyllate (4). Of these two basic skeletal types, daphniphylline is more common than secodaphniphylline. For example, 1000 kg of *D. macropodum* leaves yielded 100 g of 1 and only 1.1 g of 2.[3] Largely for this reason, we selected methyl homodaphniphyllate (3) as the first target of our synthetic investigations.

Concurrent with the final stages of the synthesis described in the foregoing paper, we began to think about the problem of *Daphniphyllum* alkaloid synthesis in a different way.[4] Examination of the skeleton of seco-



1 2 3 4

daphniphylline reveals that the unbroken squalene molecule may be traced through the pentacyclic domain. To

(1) For part 10, see: (a) Heathcock, C. H.; Davidsen, S. K.; Mills, S. G.; Sanner, M. A. *J. Org. Chem.*, preceding paper in this issue.
(2) (a) Present address: Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285. (b) Present address: Department of Chemistry, Yale University, New Haven, CT 06511.
(3) Toda, M.; Hirata, Y.; Yamamura, S. *Tetrahedron* **1972**, *28*, 1477.
(4) For a preliminary communication, see: Ruggeri, R. B.; Hansen, M. M.; Heathcock, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 8734.

0022-3263/92/1957-2544$03.00/0